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Contents

A Review on Medicated Chewing Gum

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ABSTRACT

According to the European Pharmacopoeia, Medicated chewing gum (MCG) is a non-dissolving intraoral medicine dosage form that can be used locally to treat oral disorders or systemically after being absorbed through the buccal mucosa or from the gastrointestinal tract. It can be used locally or systemically to administer drugs orally. Significant advancements in technology and research pertaining to the oral medicine administration route have been made in recent years. Because of its capacity to increase patient compliance in both pediatric and elderly patients as well as the general public, medicated chewing gum has drawn attention from all around the world this year. The manufactured product is evaluated for a number of qualities, such as colour, stickiness, hardness, and In vitro drug release. Chewing gum can be used as a transportable method of oral medicine administration, both locally and systemically. International dentistry associations, authorities, and federations have validated the benefits of sugar-free chewing gum for the mouth and teeth. Caries and gingivitis can be prevented by combining sugar-free chewing gum with floss, fluoride toothpaste, and interdental cleaners.

Keywords: Chewing gum; oral health; buccal mucosa; systemic effects.

1. INTRODUCTION

In 1924, the first medicated chewing gum was released under the Aspergum brand of United States. A new medicine delivery method called medicated chewing gum (MCG) uses an elasticgelatine basis combined with binding agents, sweeteners, and active medicinal ingredients.MCG is designed to treat mouth diseases locally or to be absorbed systematically by the oral cavity's mucosa. MCG is a solid or semisolid dosage form composed of single or more active pharmaceutical components that are either insoluble or soluble in water mixed with a lipophilic base (Indhumathi & Siva Kumar, 2020). Chewable dosage forms, such as chewing gum and chewable tablets, are made to be mechanically processed in the mouth to improve the dissolving and/or disintegration of medications.

Since chewing gums are taken orally and the oral route of drug administration is the mostpopular among patients and doctors because of its numerous advantages, they are considered to be a comfortable oral mucosal medication delivery method in recent years. Chewing gum has been used to deliver nicotineas a smoking cessation intervention (Hattab, 2023).

Definition: A MCG is form of solid dose with one or more active pharmacological ingredients, medicated chewing gum is a solid, single-dose product that is intended to be chewed for a predetermined period of time in order to deliver the medication. The oral cavity is the site of absorption for many medications (Thube, 2024).

Advantages of chewing gum:

1. You can use chewing gum anywhere, at any time, and without water.
2. When swallowed, MCG decreases the chance of overdose.
3. The product has good stability since the inserted medicinal ingredients are shielded from light, air, and water.
4. High levels of acceptance among kids and teens.
5. Dental caries: Chewing gum formulations frequently aim to prevent and treat oral illness.

6. Systemic therapy:

(a) Muscle aches, headaches, and minor discomfort can all be effectively treated.

(b) Give Up Smoking Clinical trials have been conducted on nicotine, lobeline, and silver acetate-containing chewing gum formulations as smoking cessation aids (Nasseripour et al., 2021).

Disadvantages of chewing gum:

• Speed and chewing style affect medication release. The way the patient chews the MCG formulation greatly affects how much medication is released from the MCGs. Compared to all chewing speeds, a single chew per second produced a noticeably greater release of nicotine from the cigarette gum.

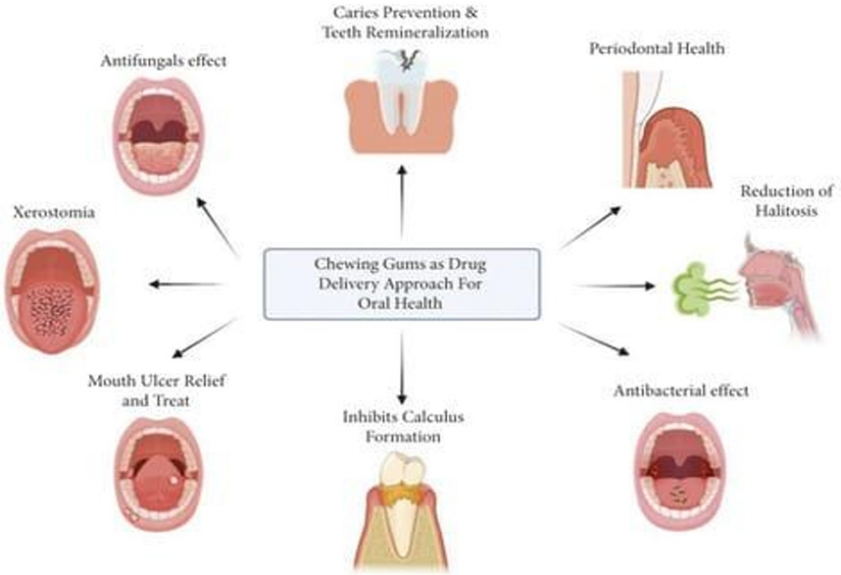

Fig. 1. MCG for oral health

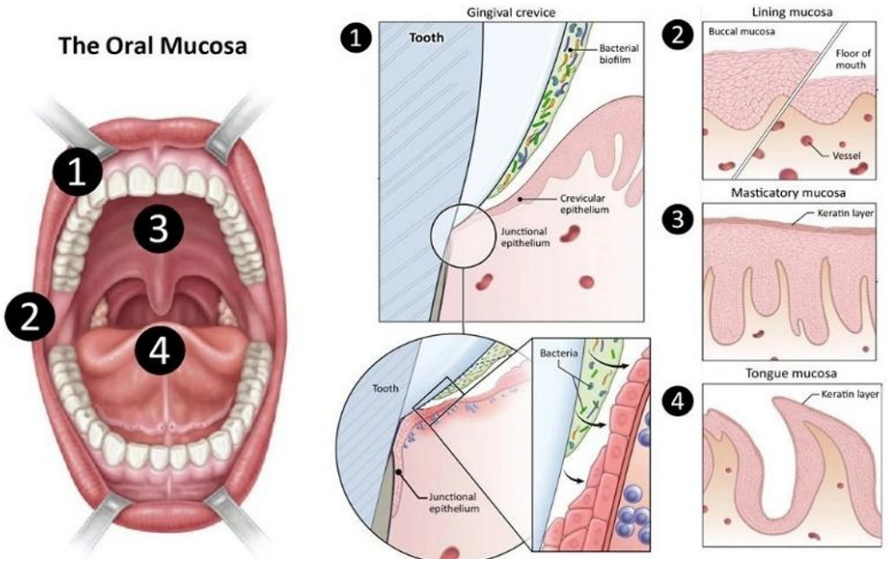

Fig. 2. Oral mucosa

• MCG retains and contacts the oral mucosa for a longer period of time. The medication is progressively released into saliva when it is chewed.

• The inclusion of sorbitol in certain formulations may also result in flatulence, gastric ulcers, and stomach irritation from constant salivary swallowing. 2. The size of the particles in the medication should be maintained below roughly 100 micrometers to prevent an undesirable gritty sensation while chewing (Squier, 1991). The drug's physical characteristics include:

• Artificial sweeteners can cause allergic responses.

• The risk that young toddlers could choke after ingesting gum (Conway, 2003).

Absorption of drug across the oral mucosa:

Oral medication formulations enter the mouth through the oral cavity, however their contact with the oral mucosa is brief. At about 100 cm2, the overall area available for medication absorption is very small. A speedy initiation of action and quick achievement of high blood levels are made possible by the mouth cavity's abundant supply of lymphatics and blood arteries. Oral dose formulations frequently have the same bioavailability as their intravenous counterparts, therefore aseptic preparation is not necessary. A medication must dissolve in saliva in order to be absorbed orally. In the absence of a particular delivery method that facilitates contact with the mucosa, very hydrophobic compounds are likely to be swallowed whole and will not dissolve sufficiently (Imfeld, 1999).

Optimal criteria for drug profile:

1. The medication must not possess any unpleasant flavour, as this can impact how consistently patients adhere to the treatment.

2. The size of the particles in the medication should be maintained below roughly 100 micrometers to prevent an undesirable gritty sensation while chewing (Squier, 1991).

The drug's physical and chemical characteristics include:

• High salivary solubility and chemical
• PH-independent solubility
• Tasteless patient-related factors
• Non-carcinogenic
• Non-toxic to the oro mucosa and salivary duct
• Not likely to promote decay of teeth or discolour the oral mucosa
• Not likely to alter the rate of salivary flow;

2. MCG MANUFACTURING PROCESSES

There are primarily three ways to manufacture MCG, as listed:

1. Conventional or Traditional Method (melting)
2. The Method of Cooling, Grinding, and Tableting
3. Direct Compression

Conventional or traditional method (melting):

The traditional method involves cutting the bark of the sapodilla tree to remove the chicle, which is then burned over an open flame to eliminate any remaining moisture it is put into wooden molds, formed into blocks, then dried with hot air before being melted and softened once it reaches a consistency like to chunky toffee. The mixture is then moved to a kettle blender, where it is gradually supplemented with corn syrup, active substances, bulking agents, sweeteners (such powdered sugar), and other excipients, such as fruity flavours. Next, a thin, broad ribbon is formed out of the chewing gum. To stop adherence, a thin layer of finely powdered sugar is applied during this stage. After that, the gum is kept in the refrigerator for two days to guarantee adequate curing. It is then finally chopped to the appropriate size (Ezhumalai et al., 2011).

The method of cooling, grinding, and tableting: This method involves melting the gum base in an oven first, then mixing it with the other chewing gum ingredients together. Either adding a coolant, like solid carbon dioxide, or submerging the apparatus in a cold liquid, such as liquid nitrogen, cools the mixture during the mixing stage until it forms into a hard, brittle mass.

This process makes it easier to ground the gum's ingredients into a thin powder for chewing gum. The main reason of the grinding procedure is challenging is that chewing gum particles have a tendency to stick to the grinding apparatus. By adding a grinding aid, such as maltodextrin or an alkaline metal phosphate, at a concentration of 2–8% by weight, this problem can be lessened. The gum powder is then mixed with additional excipients and active substances, such as vitamins, minerals, or herbal components. After that, this mixture is ground into granules that can be molded into different chewing gum products or compressed into tablets.

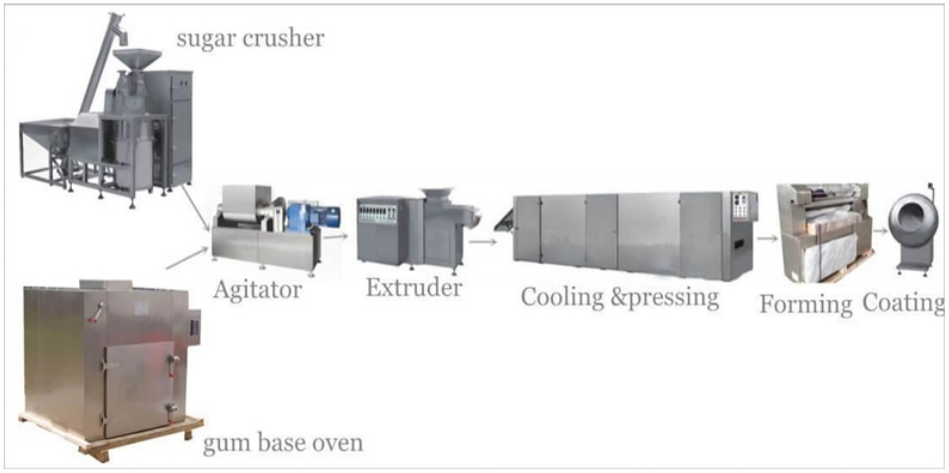

Fig. 3. Schematic representation of chewing gum manufacturing

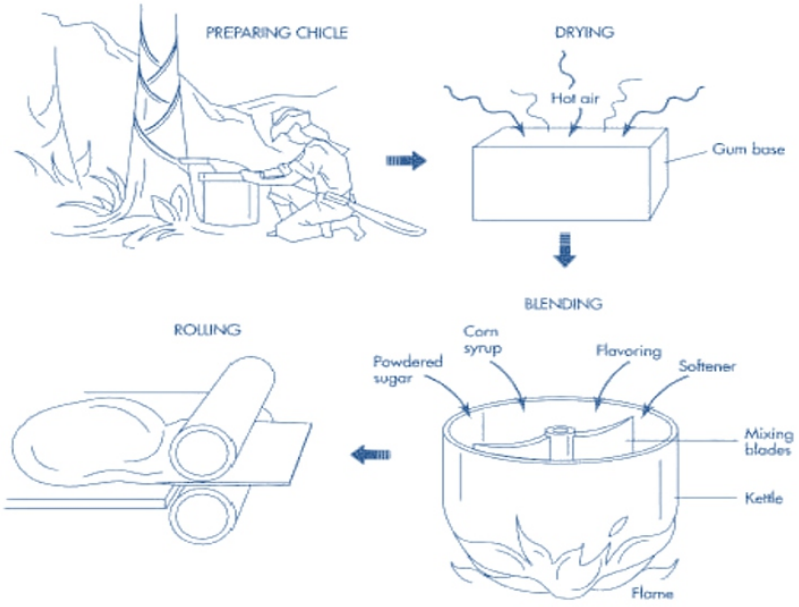

Fig. 4. Direct compression method

Direct compression method: Chewing gum tablets are made using the direct compression technique, which uses specially prepared compactable gum components in powdered form. A sizable amount of inert soft thermoplastic elastomers, a mixture of polyols (such as sorbitol, xylitol, and mannitol), sugars, plasticizers, and anti-caking agents make up these co-processed gum bases, which are intended for direct compression. Health in Gum® compresses to create items that look like prescription tablets.

Compared to medicated chewing gum which is made using conventional techniques, these pillsare harder and have a more brittle texture. Additionally, their impact on the release of active pharmaceutical ingredients (APIs) is noticeable. For example, nicotine gums produced via direct compression have a faster rate of release than Nicorette® made using traditional methods. HiG PWD-01, HiG PWD-03, and HiG PWD-04 are the three different grades of Health in Gum® that comprise 25%, 35%, and 30% gum base, respectively. The active molecules in these grades have a longer shelf life because of their lower moisture content (Kumar & Solanki, 2018).

Composition of medical chewing gum:

Table 1. Water insoluble gum base – plasticizer, elastomers, elastomeric solvents, fillers (Athanikar & Gubler, 2004)

Ingredients	Purpose	Example
Plasticizers	To achieve a range of appealing textures and consistency characteristics.	Lanolin, palmitic acid, oleic acid, stearic acid, glycerine, hydrogenated vegetable oils.
Elastomers	Offers flexibility and manages the gummy consistency.	Natural- chicle gum, nispero,) Synthetic rubbers- (butadiene, styrene)
Fillers or texturisers	Provides texture	Caco3
Mineral adjuvant	Enhance the ability to chew and offer a suitable size for the gum piece with a minimal dosage of medication.	Magnesium carbonate, aluminium hydroxide, talc, aluminium silicate.

Table 2. Water soluble gum base- sweeteners, antioxidants, softener and emulsifier, colorants and whiteners, flavouring agents, bulking agent, compression adjuvant (Pedersen & Rassing, 1990; Christrup & Moeller, 1986)

Ingredients	Purpose	Example
Sweeteners	To achieve the intended level of sweetness in the product.	xylose, sucrose, aspartame, alitame etc.
Anti oxidants	Prevents microbial growth	BHT, BHA,propyl gallate
Softeners and emulsifiers	These components are incorporated into the chewing gum to enhance its chewability and overall mouthfeel.	Glycerin, lecithin, tallow, hydrogenated tallow, mono/di/ tri glycerides
Colorants and whiteners	Enhances the formulation's tolerability and adds a calming colour.	Titanium dioxide, natural food colours and dyes suitable for food, drug and cosmetic applications
Flavouring agents	To increase consumer acceptance	Essential oils (citrus oil, fruit essences, peppermint oil, mint oil, clove oil) and synthetic or artificial Flavors
Bulking agents	This is utilized when a low-calorie gum is preferred.	Polydextrose, oligofructose, inulin, indigestible dextrin
Compression adjuvant	To ease the compression process	Silicon dioxide, magnesium stearate, calcium stearate, talc

3. EVALUATION OF MCG

Visual appearance: To assess the prepared MCG samples' flavour, consistency, coloration, texture, and clarity, a visual inspection was conducted. Thickness measurement: Each prepared gummy's mean thickness was measured using a digital vernier calliper (screw gauge in milliliter) (Jacobsen et al., 1999).

Weight variation: A computerized electronic balance was used to determine each prepared gummy's mass, and the average and standard deviation were then calculated for each gummy.

Percentage moisture loss and moisture content: After being weighed, each gummy was kept for three days in a desiccator with around one gram of anhydrous calcium chloride. The gummies were taken out of the desiccator and weighed once again after this time. The following formula was used to determine the moisture content and the percentage of moisture loss.

Percentage moisture loss = Initial weight – Final weight/Initial weight

Percentage moisture content = Initial weight – Final weight

Hardness test: The Monsanto hardness tester was used to determine the forces needed to crush the gummy in order to determine its hardness (Daharwal et al., 2013).

Surface pH: A digital pH meter is used to measure the gum's pH after it has been divided into four segments and submerged in 50 milliliters of distilled water for ten minutes.

Drug content: 50 mL of 0.1 N HCl solution was added to a beaker containing the gummy, and it was magnetically stirred for two hours. A UVvisible spectrophotometer was then used to determine the drug content after the solution had been filtered via Millipore filter paper (Khairnar et al., 2016).

In vitro drug release study: This examination is conducted utilizing an appropriate volume of 0.1 N HCl at a temperature of 37°C, with the dissolution apparatus type II operating at a rotation speed of 50 rpm. At specified time intervals, a sample is extracted from the jar and substituted with an equivalent volume of the dissolution medium after filtration. The sample is then analyzed at its maximum absorbance using a UV-visible spectrophotometer (Naik & Gupta, 2011).

Therapeutic uses: The primary focus of MCG formulation is the prevention and treatment of oral disorders. This gum is intended to provide a localized and long-lasting effect by releasing medication at a regulated rate over a prolonged period of time. As an additional measure for oral hygiene after meals and snacks, sugar-free MCG is used to promote dental health. MCG is also used in drug delivery systems for systemic effects, especially when the medicine is absorbed through the buccal cavity's mucosal lining. This reduces the possibility of gastrointestinal side effects while enabling quick and efficient therapy. Additionally, medications from MCG are absorbed faster than those from conventional pills, which results in immediate pain alleviation (Doshi et al., 2006).

Table 3. Worldwide marketed chewing gums

Trade Mark	Active Ingredient	Uses	Manufacturer	Picture
Nicorette®	Nicotine	Smoking Cessation	GlaxoSmithkline	
Nicotinelle®	Nicotine	Smoking Cessation	Novartis Consumer Health	
Chooz®	Calcium Carbonate	Stomach acid neutralization	Leosons Overseas Corporation, USA	
Stay Alert®	Caffeine	Alertness	Stay Alert Safety Services, Inc	
Fluorette®	Fluoride	Cariostatic	Fertin Pharma A/S	
Vitaflo CHX®	Chlorhexidine	Preventing tooth decay	Fertin Pharma A/S	

Travvel®	Dimenhydrinate	Motion sickness	Asta Medica	

4. APPLICATIONS

Dental caries:

• The development of chewing gum formulations aims to prevent and treat oral diseases.

• By controlling the rate at which active chemicals are released, these formulations can guarantee a long-lasting local effect.

• Furthermore, they contribute to the restoration of the pH balance in dental plaque, thereby diminishing both the intensity and occurrence of dental caries.

• Fluoride-containing chewing gum has been shown to be successful in avoiding dental cavities in xerostomia patients of all ages.

• Additionally, chewing gum containing chlorhexidine helps treat diseases like gingivitis, periodontitis, and infections of
the pharynx and mouth.

• It also serves to inhibit plaque formation.

• The formulation of chewing gum containing chlorhexidine offers several benefits, such as homogeneous dispersion throughout the oral cavity and less tooth discoloration.

• Furthermore, a chewing gum formulation can successfully conceal the disagreeable taste of chlorhexidine (Mehta et al., 2011).

Systemic therapy:

• **Pain:** Muscle aches and headaches are among the mild discomforts that chewing gum may help to relieve.

• **Smoking cessation:** The formulation of chewing gum that incorporates nicotine and lobeline has undergone clinical testing as a supportive measure for individuals attempting to quit smoking (Banakar et al., 2022).

Obesity: It has been shown that active ingredients including caffeine, guarana, and chromium are useful in the treatment of obesity. By improving blood glucose homeostasis, chromium in particular is said to reduce food cravings.

Other indications: For a number of ailments, including xerostomia, allergies, motion sickness, acidity, colds and coughs, diabetes, and anxiety, chewing gum may be a useful medication administration method (American Dental Association, 2023).

5. CONCLUSION

Since self-administration is possible, medicated chewing gum is regarded as a good drug delivery strategy. When compared to other oral dose forms, it offers numerous benefits. Chewing releases the active pharmaceutical substance from the gums, which is then absorbed by the buccal mucosa. It is used to treat dental caries, local oral illnesses, elevated alertness, cognitive functions, and quitting smoking. It can be concluded that patients are beginning to embrace the use of chewing gum.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Stability Evaluation of Acetylsalicylic Acid in Commercial Aspirin Tablets under Different Storage Conditions

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A B S T R A C T

This study evaluated the stability of acetylsalicylic acid (ASA) in commercial Aspirin Protect 100 mg tablets under eight different storage conditions, including varying exposure to moisture, light, and temperature, with a focus on tablets stored in dosette boxes. Acid-base titration methods were used to assess ASA degradation and stability. Elevated moisture had the greatest impact on ASA stability, significantly reducing recovery factors to 85.38% and 81.10% under high humidity, while temperature influenced ASA stability, with notable deviations from control values at temperatures above 25°C (13.26% and 7.16% for two methods). Although storage at 18–25°C yielded acceptable results, reduced temperatures (<8°C) provided better stability. Direct sunlight exposure caused further degradation, reducing recovery values to as low as 82.5% and increasing deviations from control (-10.82% to -16.77%). Hydrolysis, exacerbated by environmental factors, was identified as the primary degradation pathway, leading to the formation of salicylic acid and acetic acid. Samples stored in under recommended conditions had the best stability, with recovery factors meeting pharmacopoeia standards (101.08% and 99.16% of labelled content). These findings underscore the importance of proper storage practices for ASA tablets to maintain their quality, safety, and therapeutic efficacy. While repackaging tablets into dosette boxes may improve compliance, it can compromise stability, highlighting the need for stricter storage guidelines to ensure optimal patient outcomes.

Keywords: Acetylsalicylic acid; acid-base titration; dossete boxes; drugs' quality and stability; patient adherence and compliance.

1. INTRODUCTION

Acetylsalicylic acid (ASA) is an active pharmaceutical ingredient (API) in Aspirin tablets, also known by its IUPAC name as 2acetoxybenzoic acid. It is an organic molecule with carboxyl (-COOH) and acetyl ester (OCOCH3) groups attached to the aromatic benzene ring. Organoleptic properties include

its colour and appearance as white crystalline powder or crystals, with a sour taste and characteristic slightly vinegar-like odour. While remains stable in dry conditions, exposure to increased humidity rapidly induces hydrolysis, decomposing the molecule into two acids, salicylic and acetic (Fig. 1). The forced ASA degradation study performed by Kowalska et al., (2022) and Urich et al., (2023) confirmed that acetylsalicylic acid can be decomposed to salicylic acid under the influence of high temperature, acidic, alkaline, oxidative, and hydrolytic conditions.

Synthesized in the late 19th century, this weak acid become widely used as a painkiller and, by the mid-20th century, became the most popular analgesic in the world, according to the Guinness World Records (Kosinski et al., 2018). Today, Aspirin is well-known not only for its analgesic, but also for its anti-inflammatory, antipyretic, and antiplatelet properties. In fact, by the end of 20th century, researchers discovered that low doses of this medication can reduce the risks of heart attacks and strokes. Inhibition of platelet cyclooxygenase (COX)-1 activity followed by inhibition of thromboxane (Tx) A2 generation and platelet aggregation is the basis of its antiplatelet effect (Gurbel et al., 2024). Additionally, recent studies have shown the wide range of possibilities ASA use in serious diseases prevention with significantly reduction in the incidence of various cancers, including colorectal, oesophagus, stomach, and breast cancers (Qiao et al., 2018; Bosetti et al., 2020; Schreinemachers et al., 1994; Thorat & Cuzick, 2013).

Due to its widespread use, maintaining the high quality, safety, and effectiveness of aspirin is crucial—from manufacturing though drug supply chain to consumption. Many patients store medications in dosette boxes (pill organizers), to keep track of their use. These organizers are convenient for medication adherence and are often kept in visible locations, such as shelves, tables, bags, bathroom cabinets, or refrigerators (Conn et al. 2015; Mylrea et al. 2012). However, storing medications as described may expose them to moisture, light, and temperature fluctuations, potentially compromising their quality and efficacy.

Storage conditions play a critical role in ensuring stability of pharmaceutical products. Improper storage can degrade the API, affecting the drug's efficacy, safety and therapeutic outcomes

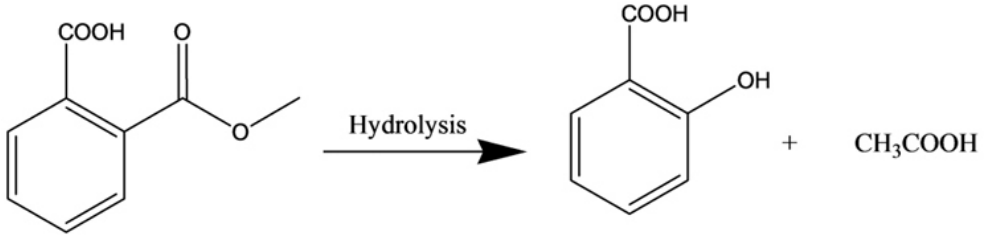

Fig. 1. The hydrolysis of ASA into salicylic acid and acetic acid

(Ansari, 2017). To preserve the integrity of pharmaceutical products, it is essential to perform qualitative/quantitative analyzes of APIs under various environmental conditions, ensuring that active compounds remain stable and effective until the product's expiration date.

A variety of analytical techniques are used to evaluate the impact of external conditions on drug quality. While modern analytical techniques with advanced instrumentation are indispensable for drug quality control, traditional methods retain their importance, particularly in resource-limited settings. Traditional techniques, such as acidbase titration, are cost-effective and require minimal resources compared to sophisticated instrumentation. Acid-base titration is widely employed for the precise quantitative analysis of ASA, verifying the aspirin content in pharmaceutical formulations and ensuring product quality and efficacy.

This study aimed to evaluate the effects of different storage conditions—including moisture, different temperatures, and light exposure—on the stability of acetylsalicylic acid tablets stored in dosette boxes. The study utilized simple acidbase titration methods to assess any degradation and quantify the stability of the tablets under varying conditions.

2. MATERIALS AND METHODS

2.1 Materials

Ethanol (C_2H_5OH) (Sigma Aldrich, USA), sodium hydroxide (NaOH) (Sigma Aldrich, USA), phenolphthalein indicator (Sigma Aldrich, USA), Aspirin Protect 100 mg tablets (Bayer, Germany), hydrochloric acid (HCl) (Sigma Aldrich, USA), chloroform (CH_3Cl) (Sigma Aldrich, USA), and distilled water were used in the study.

2.2 Instruments and Equipment

An analytical balance AX120 (Shimadzu), a magnetic stirrer, a Sonorex ultrasonic bath (Bandelin electronic Gmbh & Co. KG), standard laboratory titration equipment, and a distillation water still (GFL Gesellschaft Fuer Labortec) were employed.

2.3 Samples and Storage Conditions

A total of 320 Aspirin tablet samples were divided into four groups to monitor the impact of temperature,

humidity, and light on drug quality (Table 1). The control sample (U8) was stored according to the manufacturer's recommendation (in the medication's external and internal packaging, protected from moisture and sunlight, at room temperature). All samples were exposed to different storage conditions for 30 days.

2.4 Acid-Base Titrations

Acid-base titrations are used for the quantitative analysis of pharmacodynamically active substances that, due to their chemical nature, act as acids or bases. These titrations are performed by dissolving the analyte (acid or base) and the titrant (base or acid) in water or non-aqueous

Table 1. Storage conditions of the Aspirin tablet samples

Parameter		Storage location	Sample ID
Temperature	>25°C	Kitchen (near oven)	U1
	18-25°C	Bedroom (nightstand)	U2
	<8°C	Kitchen (refrigerator)	U3
Humidity	increased	Bathroom (cabinet)	U4
	moderate	Bedroom (nightstand)	U5
Light	direct sunlight	Living room	U6
	darkness	Bedroom (nightstand)	U7
Under recommended storage conditions		Original pharmaceutical package	U8

solvent. Slightly modified pharmacopeial procedures for the acid-base titration of acetylsalicylic acid (ASA), adapted to suit the specific needs of the study (USP, 2006; EDQM, 2024). Two independent titration methods were applied, as described in the following sections.

Each titration method was repeated three times per sample, and the results are expressed as mean ± SD. The results obtained under various experimental storage conditions were compared to those from samples stored under the recommended conditions. The content of the API in the Aspirin tablets was calculated relative to the labelled content and expressed as a percentage, as shown in Equation (1).

$$\text{recovery factor (\%)} = \frac{\text{practical ASA content}}{\text{labeled ASA content}} \cdot 100 \quad (1)$$

To evaluate the impact of different storage conditions, the deviation in API content was calculated by comparing the tested samples to the control sample stored under recommended conditions, as shown in Equation (2).

$$\text{Deviation (\%)} = \frac{\text{sample ASA content} - \text{control ASA content}}{\text{control ASA content}} \cdot 100\% \quad (2)$$

Titration with 0.5 M HCl solution:

o Ten Aspirin Protect 100 mg tablets were weighed and ground finely using a mortar.
o The mass of powder equivalent to 500 mg of acetylsalicylic acid was weighed and dissolved in 10 mL ethanol (96%) in an Erlenmeyer flask with a glass stopper.
o 50 ml of 0.5 M NaOH solution was added. After one hour, the solution was titrated with 0.5 M HCl using 0.2 ml of phenolphthalein solution as an indicator.
o Meanwhile, a blank sample was prepared and titrated.
o The consumption of 1 mL of 0.5 M HCl corresponds to 45.04 mg of acetylsalicylic acid.

Titration with 0.5 M NaOH solution:

o Ten tablets of Aspirin Protect 100 mg were ground in a mortar.
o The amount of tablet mass containing 150 mg of acetylsalicylic acid was weighed.
o To the weighed amount of acetylsalicylic acid, 10 ml of chloroform was added.
o The mixture was mixed for 5 minutes in an ultrasonic bath and filtered through filter paper to remove any undissolved particles.
o After filtration, 5 mL of distilled water and 5 drops of phenolphthalein indicator solution were added to the filtrate.
o Titration was performed with 0.1 M NaOH until a persistent pink colour appeared.
o The amount of 0.1 M NaOH used corresponds to the acetylsalicylic acid content.
o 1 mL of 0.1 M NaOH corresponds to 0.02212 g of acetylsalicylic acid.

3. RESULTS AND DISCUSSION

3.1 Temperature Impact

The data obtained from the acid-base titration assays presented in Table 2 highlight the impact of temperature on the quantitative API content in Aspirin Protect 100 mg tablets. As shown in the Table 2, the largest deviations from the control values were observed when the tablets were exposed to temperatures above 25°C, with a 13.26% deviation for method I and 7.16% for method II. The recovery factor, which accounts for the labelled API content, was 114.40% and 106.27%, respectively.

While it was expected that the best match with the control values of API content in aspirin tablets would be achieved when stored at a temperature of 18-25°C, it is noteworthy that even better results were

obtained for reduced temperatures <8°C. This is probably due to the slowing down the hydrolysis rate of ASA at lower temperatures, as demonstrated by studies using variable-temperature kinetics (Alibrandi et al., 1996). This is further confirmed by the recovery factor results, which showed improved values for both methods at lower temperatures. The obtained results can be attributed to the possible influence of other factors, as the tablet samples were not stored in the original medication packaging but rather placed in dosage boxes. Additionally, Mamede et al., (2006) reported that API in Aspirin tablets can interact with excipients when exposed to different temperatures. Thermal analysis revealed differences in decomposition temperatures compared to pure ASA, suggesting possible impacts on its pharmacological activity and physicochemical properties. Proper storage conditions, including not only the temperature range but also factors such as light, humidity, microbiological purity, pressure, and ventilation, are essential to maintain the quality of pharmaceutical products (Shafaat et al., 2013; Ali et al., 2022).

Table 2. Impact of temperature on the quantitative content of ASA in Aspirin tablets

Sample ID	Temperature (°C)	ASA (mg) content ± SD[a]		Recovery factor (%)		Deviation (%)	
		Method I	Method II	Method I	Method II	Method I	Method II
U1	>25	572.00±0.02	159.40±0.12	114.40	106.27	13.26	7.16
U2	15-25	463.90±0.01	137.10±0.02	92.80	71.40	-8.15	-7.83
U3	<8	477.40±0.03	143.78±0.02	95.40	85.80	-5.47	-3.33
U8	15-25[b]	505.04±0.13	148.74±0.03	101.08	99.16	n/a[c]	

a n=3, SD – standard deviation

b Control sample stored under recommended storage conditions.

c n/a – not applicable

To ensure the quality of pharmaceutical products, controlled storage and transit conditions are necessary, especially when changes in quantitative content or loss of potency may affect the efficacy and safety of medications. Temperature changes during the storage of ASA can significantly impact on its stability. Some et al., (2001) reported that ASA undergoes temperature-dependent hydrolysis, affecting its pharmacokinetics, stability and pharmacodynamic properties. Additionally, increased pressure at room temperature is a crucial factor, especially since polymorphic transformation of ASA can occur, leading to structural and physicochemical changes in the molecule (Ali et al., 2022).

3.2 Humidity Impact

High humidity in storage conditions can significantly impact the stability and degradation of Aspirin tablets. Studies by Yamazaki et al., (2010; 2011) have demonstrated that when humidity exceeds 55%, the decomposition rates of Aspirin tablets increase, leading to colour changes. This not only affects the drug's quality but also reduces patient compliance. Further research by Veronica et al. (2020; 2022;

2024) revealed that the choice of excipients in Aspirin tablet formulations can play a crucial role in how the drug holds up in high-humidity environments. Among the excipients studied, crospovidones and cellulose were found to significantly accelerate the degradation of Aspirin (Ougi et al. 2020; Höckerfelt & Alderborn, 2014). These findings emphasize the importance of understanding how humidity affects the stability of medications, especially when formulating moisture-sensitive drugs like aspirin and storing them properly.

In the present study, the results from both acidbase titration methods show negative deviations when compared to the control sample stored under recommended conditions (Table 3). Both samples (U4 and U5) were stored in dosette boxes, outside of their original packaging. When comparing samples exposed to normal versus increased humidity, it is evident that elevated humidity accelerates the deterioration of Aspirin tablets quality. The significant decrease in recovery factors for sample U5 (85.38% and 81.10%) under increased humidity conditions underscores Aspirin's sensitivity to moisture. Even when stored in normal humidity, the samples stored in dosette boxes exhibited recovery factors below the acceptable range (94.50% and 89.90%), indicating that the lack of original packaging still allowed some degradation. The ester functional group in the structure of acetylsalicylic acid is a key factor contributing to its instability, as esters are highly susceptible to hydrolysis under a variety of conditions, both in vivo and in vitro. When exposed to moisture, hydrolysis occurs, resulting in the release of salicylic acid and acetic acid (Fig. 1).

These results are similar to those reported by Mylrea et al., (2012) which suggest that Aspirin underwent partial hydrolysis to salicylic acid, likely due to improper storage conditions, such as removing the tablets from theiroriginal packaging and storing them in dosette boxes. This contributed to the observed deterioration in quality and recovery factors. However, the degradation of ASA not only compromises the quality of the drug but also results in the formation of degradationproducts that can exert significant toxicological effects Salicylic acid, formed by hydrolysis of ASA in the gut, is a proven teratogen in animals. Further, exposure to salicylic acid after ingestion has been associated with reproductive and developmental toxicity (Andersen, 2003).

Table 3. Impact of humidity on the quantitative content of ASA in Aspirin tablets

Sample ID	Humidity	ASA (mg) content ± SD[a]		Recovery factor (%)		Deviation (%)	
		Method I	Method II	Method I	Method II	Method I	Method II
U4	Normal	472.90±0.01	134.90±0.11	94.50	89.90	-6.36	-9.30
U5	Increased	426.90±0.07	121.60±0.14	85.38	81.10	-15.47	-18.25
U8	Normal[b]	505.04±0.13	148.74±0.03	101.08	99.16	n/a[c]	

a n=3, SD – standard deviation

b Control sample stored under recommended storage conditions.

c n/a – not applicable

Table 4. Impact of sunlight on the quantitative content of ASA in Aspirin tablets

Sample ID	Light	ASA (mg) content ± SD[a]		Recovery factor (%)		Deviation (%)	
		Method I	Method II	Method I	Method II	Method I	Method II
U6	Direct sunlight	450.40±0.03	123.80±0.04	90.00	82.50	-10.82	-16.77
U7	Dark	486.40±0.07	137.10±0.01	97.20	91.40	-3.69	-7.83
U8	Dark[b]	505.04±0.13	148.74±0.03	101.08	99.16	n/a[c]	

a n=3, SD – standard deviation

b Control sample stored under recommended storage conditions.

c n/a – not applicable

3.3 Sunlight Impact

In their study, Al-Maydama et al., (2018) treated Aspirin with gamma rays, UV rays, and direct sunlight at a temperature of 40°C with varying exposure times. Their results showed that ASA samples treated at 40°C under UV exposure for 12 hours exhibited the lowest thermal stability and activation energy. Similarly, Daescu et al., (2021) demonstrated that UV light can cause photodegradation of ASA in aqueous solution. They compared the hydrolysis reaction of ASA with or without excipients in a 0.3 M phosphate buffer solution at different pH values. Their findings indicated that pure ASA exhibited a gradual increase in the intensity of photoluminescence excitation spectra and a decrease in photoluminescence emission. In contrast, ASA with excipients exposed to UV light underwent a phototautomerization process, yielding different outcomes attributed to the presence of salicylic acid.

The results from the present study indicate that direct sunlight exposure influenced the stability and integrity of Aspirin tablets (Table 4). The observed decrease in recovery values (90.00% and 82.5%) and the increased negative deviation from the control (-10.82% and -16.77%) suggest that sunlight accelerates the degradation of ASA in the commercial tablets. The quantitative analysis of ASA in sunlight-exposed samples revealed notable changes (450.40±0.03 mg versus 500.00 mg labelled, and

123.80±0.04 versus 150.00 mg labelled), highlighting the influence of environmental factors, such as UV radiation. As previously noted the hydrolysis of ASA, potentially exacerbated by the heat and sunlight, may lead to the conversion of API into salicylic acid and acetic acid, thereby reducing the tablets' potency.

Samples stored in a dark place and protected from UV radiation yielded results, particularly those analyzed using Method I, which complied with the pharmacopoeia requirement that ASA content should fall within 95 to 105% of the labelled amount. A review of the literature reveals a notable lack of studies addressing the impact of sunlight exposure on stability of ASA in pharmaceutical products. These findings underscore the need for further research to provide recommendations and guidelines for the storage and handling of ASA tablets to prevent degradation and ensure optimal patient outcomes.

4. CONCLUSION

While repackaging Aspirin Protect 100 mg tablets into dossete boxes can enhance medication adherence and patient compliance, it may also significantly impact their stability. ASA, being a hydrolysable molecule, shows reduced stability when exposed to varying environmental conditions in dossete boxes.

The study findings revealed that elevated moisture levels had the most significant effect on the stability and quantitative content of ASA, followed by light and temperature. Notably, the best recovery results (101.08% and 99.16%) were observed in samples stored under the manufacturer's recommended conditions. These results underscore the critical importance of proper storage practices for ASA tablets to maintain their quality, safety, and therapeutic efficacy, which are easily compromised under suboptimal conditions.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

The author(s) hereby declare that generative AI technology, specifically ChatGPT, was utilized during the proofreading of the manuscript. The details of the AI technology, including its version, model, source, and input prompts used, are provided below to ensure transparency in its application:

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The generative AI was used exclusively for proofreading and language editing purposes. No generative content (e.g. text, ideas, pictures, or data) was introduced that was not explicitly provided by the authors. The AI's suggestions were carefully reviewed and integrated manually by the authors to ensure alignment with the original intent and integrity of the manuscript.

CONSENT AND ETHICAL APPROVAL

This study did not require approval from an ethics committee, as it did not involve direct participation of patients or their inclusion as subjects of investigation. The research was exclusively focused on analytical aspects. Consequently, obtaining written informed consent from patients or volunteers was not applicable.

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COMPETING INTERESTS DISCLAIMER

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Assessment of Knowledge, Attitude, and Practice of Selected Community Pharmacists towards the Disposal of Unused and Expired Medicines at Kalaburagi City

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ABSTRACT

Purpose: Disposing of unused and expired drugs presents a critical challenge with far-reaching implications for public health and environmental well-being. This issue has gained increasing attention as pharmaceutical consumption rises globally. Improper disposal practices can contaminate water bodies, soil, and ecosystems, endangering human and aquatic life. Hazards to human and environmental health and safety are high when pharmaceuticals that have been used and are no longer needed are not properly disposed of. This is why the current research is an effort to gather data on the understanding of Kalaburagi City's community pharmacists regarding proper disposal of leftover and expired medications.

Methodology: The study was conducted in various areas and colonies of Kalaburagi city, over six months from March to August 2023 for evaluating opinions with regards to disposing of unwanted medicines. Tools and teaching aids used for the study are specially designed pretested and validated questionnaires, leaflets, and videos. The study design used is "A case-control study". The inclusion criteria were, Pharmacists willing to participate, Government pharmacists, and Private pharmacists. The exclusion criteria were, Pharmacists who were not interested in participating, and person without a pharmacy background. The survey was carried out in Kalaburagi city and was divided into two groups North (test) and South (control). The test group received counseling regarding the methods of disposal of unused and expired medicines and leaflets, whereas the control group received only leaflets.

Results: A study of 461 pharmacists found that 79% were male and 21% female, with 42.3% aged 31 to 40. Notably, 92% regularly check medication expiry dates, and 85% are concerned about drugs polluting the environment. An overwhelming 94% support drug take-back programs. Most pharmacists (84%) recognize improper disposal as a health risk, and 92% return expired medicines to manufacturers. For disposal methods, 49% suggest returning expired meds to pharmacists, while 10% recommend flushing and 24% advise disposal in sinks. There is a push for increased consumer awareness, with 50% wanting healthcare professionals to educate on safe disposal, and 38% advocating for government-led programs.

Conclusion: The awareness regarding, the impact of improper disposal of pharmaceutical products is still unknown. It is a cornered issue and needs to be focused on. The current methods and practices are not optimal and upgraded. Pharmacists possess knowledge regarding the proper disposal of unused and expired medicines. However, they often lack the attitude to implement these practices effectively. Lack of standardized disposal facilities, limited regulatory enforcement policies and public awareness regarding safe disposal have contributed to the gap between the knowledge and practice of pharmacists.

Keywords: Unused medicines; expired drugs; pharmaceutical disposal; public health; take-back programs; safe disposal; awareness program.

1. INTRODUCTION

Despite their critical role in human health, numerous medications include harmful compounds that, if not disposed of or handled correctly, may pollute the environment (Smith, 2002).

Incorrect disposal of pharmaceutical wastes poses a significant threat of contamination and various hazards to both humans and other animals. By consuming polluted water, humans might be exposed to or collect environmental traces and residues of medicines (Daughton, 2003). Indefinitely storing, discarding, or flushing down the toilet or typical municipal trash containers are common ways that many families dispose of unwanted, unused, or expired pharmaceuticals. You should be aware that these unofficial methods put both environment and its residents at risk of major health problems when people dispose of prescriptions that have neither been utilized or have expired (Peake et al., 2015). Both adults and children have been poisoned by medications that have expired due to improper disposal (Kolpin et al., 2002). In addition to many different types of bacteria already present in sewage, presence of medications that have passed their expiration date increases likelihood that these germs may develop resistance to antibiotics, turning otherwise innocuous bugs into dangerous pathogens (Kadam et al., 2016).

WHO'S view on disposal of medicines: WHO states that UMs should never be administered to people or animals and should be disposed of as pharmaceutical waste (World Health Organization, 1999). Patient noncompliance, pharmaceutical company promotion, doctor prescription procedures, and dispensing behaviours are all potential causes of unwanted medications. Also, people are more aware of need of obtaining medical attention, which has led to a rise in use of medicines (Insani et al., 2020). No established regulations or recommendations for disposal of wasted pharmaceuticals were discovered in earlier research that compared and contrasted the link between ecological awareness and disposal of leftover medicines in different nations worldwide (Paul et al., 2017).

INDIA'S perspective towards disposal methods: The ongoing issue of how to properly dispose of old, unused, or unwanted medications has persisted in India. Precise consequences were not understood in full up until now due to lack of thorough research on subject. No respectable legislation existed in the nation to address this issue. The waste-handling municipal corporations were unaware of its existence. People weren't organized enough to care about it, and the media didn't care either. Consequently, environmental degradation persisted and ultimately resulted in everincreasing human and environmental problems. Until expiration date stated on the medicine package, pharmaceutical items guarantee the efficacy and safety of the included medication. Under ideal storage circumstances, the drug should have retained 90% of its initial efficacy by the time it expired. Just because a drug has an

expiration date doesn't mean it will become fully ineffective or even hazardous once time limit has passed. The typical shelf life of a drug is between two and five years from date of manufacture (Expired Medications: Interesting Facts, 2017). Optimal storage conditions allowed certain medications to maintain 90% of their efficacy for at least five years after the stated expiration date, and sometimes much longer. Some medications maintained their initial effectiveness up to a decade beyond the expiration date (Thomas & Kramer, 2003). Drug resistance and therapeutic failures may be worsened if some medications, such as antibiotics, are used beyond their expiration dates (Expired Medications: Interesting Facts, 2017; Ogunshe & Adinmonyema, 2014).

Environmental threat due to pharmaceuticals: Dangerous drug disposal practices caused pollution and health problems in addition to endangering the ecosystem (Albaroodi, 2019). Field of "ecopharmacovigilance" was crucial in this regard; it is defined as follows: study and practice of identifying, assessing, comprehending, and avoiding the negative environmental impacts of medicines (Holm et al., 2013). Medicines that had expired, were unused, or were undesirable were a constant source of pollution in India. The precise consequences were unclear since there weren't enough research in this field (Mani & Thawani, 2019). The development of an appropriate disposal guideline with a monitoring system is necessary, and there has not been enough of a voice in India to advocate for the safe disposal of pharmaceutical goods. It is the responsibility of the National Formulary of India to create and disseminate information about the take-back schemes (Indian Pharmacopeia Commission, 2011).

Government initiatives addressing the issue at hand: In an effort to preserve these ecologically responsible cleaners, several governmental and non-governmental groups stepped up their game. The government of India outlawed the usage of diclofenac in veterinary medicine in an effort to restore ecological harmony (Taggart et al., 2007). But instead of focusing on eliminating any one drug, we should be investigating the root causes of chemical pollution in our ecosystems. Environmental consciousness, accessibility to official state standards, dose forms, and cultural and societal attitudes all play a role in shaping people's medicine disposal practices. Most people dispose of their old medications in the sink, toilet, or trash, but this is not an eco-friendly option. Many people do not know how to properly dispose of pharmaceuticals or how they impact environmental health, which leads to a massive buildup of unused and expired prescriptions in people's medicine cabinets (Swaroop et al., 2015). People in India are still not very knowledgeable about correct disposal, even though the FDA has published specific instructions on the matter (Food and Drug Administration, 2018).

There is a risk to the environment from drugs and their byproducts. As they dissolve in water, they raise the risk of antibiotic resistance or contamination.

2. MATERIALS AND METHODS

The study was conducted in various areas and colonies of Kalaburagi city, over six months from March to August 2023 for evaluating opinions with regards to disposing of unwanted medicines. Tools and teaching aids used for the study are specially designed pretested and validated questionnaires, leaflets, and videos. The study design used is "A case-control study". The inclusion criteria were, Pharmacists willing to participate, Government pharmacists, and Private pharmacists. The exclusion criteria were, Pharmacists who were not interested in participating, and person without a pharmacy background. The survey was carried out in Kalaburagi city and was divided into two groups North (test) and South (control). The test group received counseling regarding the methods of disposal of unused and expired medicines and leaflets, whereas the control group received only leaflets.

3. RESULTS AND DISCUSSION

Test group: The present study involves a test group, the pre-intervention mean score is 3.93 and the standard value is 1.33. After pharmacist intervention, the Post-intervention values were improved with 6.74 as the mean score and a standard value of 1.06. It was found that the Tvalue is -26.93 and with the P-value 0.0001 depicting it's statistically highly significant. Control group: The present study involves a control group, Pre-intervention mean score is 4.03 and the standard value is 1.39. In the Postintervention, as the pharmacists were not educated, the values were found to be decreased with a mean score of 3.59 and a standard value is 1.49. it was found that the Tvalue is 5.01 with the P-value 0.0001 depicting it's statistically significant, Table 1.

Test group: The present study involves a test group, in which the Pre-intervention mean score is 3.22 and the standard value is 0.89. In the Post-intervention, the values were improved with a mean score of 3.67 and a standard value is 0.52. It was found that the T-value is -6.505 and P-value is 0.0001, depicting it's statistically highly significant.

Control group: Present study involves a control group, In the Pre-intervention mean score is 3.10, and the standard value is 0.90. In the Postintervention, the values were found to decrease with a mean score of 1.55 and a standard value of 1.05. It was found that the T-value is 20.825 and P-value is 0.0001 stating that it is statistically highly significant, Table 2.

Test group: The study involves a test group. In the Pre-intervention, the mean score is 2.77 and the standard value is 1.00. In the Postintervention, the values were improved with a mean score of 4.56 and a

standard value of 1.07. It was found that the T-value is -20.10 with the P-value 0.0001 which states that it is statistically highly significant.

Table 1. Details of knowledge scores in pre and post-intervention

Details of Knowledge Assessment				
Group	**PRE (MEAN±SD)**	**POST (MEAN±SD)**	**Paired T-Test**	**P-Value**
TEST Group	3.93±1.33	6.74±1.06	-26.93	0.0001
Control Group	4.03±1.39	3.59±1.49	5.01	0.0001

Table 2. Details of attitude scores in pre and post-intervention

Details of Attitude Assessment				
Group	PRE (MEAN±SD)	POST (MEAN±SD)	**PAIRED T-TEST**	P-VALUE
TEST Group	3.22±0.89	3.67±0.52	-6.505	0.0001
Control Group	3.10±0.90	1.55±1.05	20.825	0.0001

Table 3. Details of practice scores in pre and post-intervention

Details of Practice Assessment				
Group	**PRE (MEAN±SD)**	**POST (MEAN±SD)**	**Paired T-Test**	**P-Value**
Test Group	2.77±1.00	4.56±1.07	-20.10	0.0001
Control Group	2.94±1.15	2.46±1.16	5.503	0.0001

Table 4. Compares pre and post-total kap scores in the test and control group

Total KAP Scores				
Group	PRE (MEAN±SD)	POST (MEAN±SD)	**Paired T-Test**	P-VALUE
Test Group	9.92±1.96	14.97±1.80	-30.64	0.0001
Control Group	10.07±2.29	7.59±2.59	16.197	0.0001

Control group: The study involves a control group. In the Pre-intervention, the mean score is 2.94 and the standard value is 1.15. In the Postintervention, we noticed that the values decreased, the mean score was 2.46 and the standard value was 1.16. It was found that the Tvalue is 5.503 with a P-value of 0.0001 which states that, it is highly significant, Table 3. Test group: The present study involves a test group. In the Pre-intervention, the mean score is 9.92 and the standard value is 1.96. In the Postintervention, the values were improved with a mean score of 14.97 and a standard value of 1.80. It was found that the T-value is -30.64 with a P-value of 0.0001 which states that, it is highly significant. Control group: The present study involves a control group. In the Pre-intervention, the mean score is 10.07 and the standard value is 2.29. In the Post-intervention, the values were decreased with a mean score of 7.59 and a standard value of 2.59. It was found that the T-value is 16.197 with a P-value of 0.0001 which states that, it is highly significant, Table 4.

• A total number of 461 pharmacists were included in our study, out of which, we randomly selected the North and south group naming them as test and control group respectively. The test group contains 231

pharmacist and the control group contains 230 pharmacists.

• In the test group, about 231 pharmacists in the pre-intervention and in the post- intervention we had 229, 2 dropouts were seen in the test group.

1. In Kalaburagi city, out of 231 pharmacists about 209 (90.4%) of the pharmacists told that they check the expiry date of the medicines before purchasing, 14 (6.06%) do not check the expiry date of the medicines and about 8 (3.46%) however, don't know about it, in Pre-intervention. In the Post-intervention, there were two dropouts, out of 229 pharmacists, about 212 (92.2%) check the expiry date of the medicines before purchasing, 17 (7.42%)did not check the expiry date. This shows after educating the pharmacists about the need to check the medicines was improved as most of the pharmacists check the expiry of the medicines.

2. Out of 231 pharmacists, In Pre- intervention, 133 (57.57%) knew how to dispose of nearly expired medicines, 62 (26.8%) did not know how to dispose of the nearly expired medicines and 36 (15.5%) do not know about the disposal of nearly expired medicines. In the Postintervention, out of 229, 192 (83.8%) knew how to dispose of nearly expired medicines, 37 (16.1%) did not know how to dispose of the nearly expired medicines. This shows that the pharmacists knowledge was improved in the post intervention.

3. It is interesting to know in Pre-intervention, 75 (32.4%) currently had unused medications stored at their pharmacies, 113 (48.9%) did not store any unused medications stored at their pharmacies and 43 (18.6%) do not know whether they stored any unused medications at their pharmacies. In Post-intervention, 35 (15.2%) currently had unused medications stored at their pharmacies, 192 (83.8%) did not store any unused medications stored at their pharmacies and 2 (0.87%) do not know whether they stored any unused medications at their medications. This clearly indicates, Post-intervention the pharmacists knowledge enhanced about the storage of the unused medications currently.

4. While interacting with the pharmacists, out of 231 in Pre-intervention, 116 (56.2%) said they knew about average shelf life of the medicines, 76 (32.9%) did not know about the average shelf life, 39 (16.8%) don't know about it. In the postintervention, 26 (11.3%) knew about average shelf life of the medicines, 201 (87.7%) did not know about the average shelf life and 2 (0.87%) knew anything about it.

Table 5. Details of knowledge scores given by the pharmacists to questionnaires in the test group

SL. NO	Questionnaires	Pre-Intervention			Post-Intervention		
		Yes	No	Don't Know	Yes	No	Don't Know
1	Before buying any medications, do you make sure to check their expiration date?	209	14	8	212	17	0
	Percentage%	90.4	6.06	3.46	92.5	7.42	0
2	Do you know the procedure for disposing of nearly expired medicines?	133	62	36	192	37	0
	Percentage%	57.57	15.5	15.5	83.8	16.1	0
3	Does your pharmacy presently contain any drugs that you do not intend to use?	75	113	43	35	192	2
	Percentage%	32.4	48.9	18.6	15.2	83.8	0.87
4	Do you know the average shelf life of the medicines?	116	76	39	26	201	2
	Percentage%	50.2	32.9	16.8	11.3	87.7	0.87
5	Are you aware that medications have the potential to harm the environment?	175	47	9	195	34	0
	Percentage%	75.7	20.3	3.89	85.1	14.8	0
6	Have you ever gotten instructions on what to do with old or unwanted medications?	114	68	49	44	184	1
	Percentage%	49.3	29.4	21.2	19.2	80.3	0.43
7	Do you dispose of leftover medicines monthly?	153	59	19	42	187	0
	Percentage%	66.2	25.5	8.22	18.3	81.6	0
8	Do you know different guidelines for the safe disposal of drugs?	109	71	51	41	188	0
	Percentage%	47.1	30.7	22.07	17.9	82.09	0

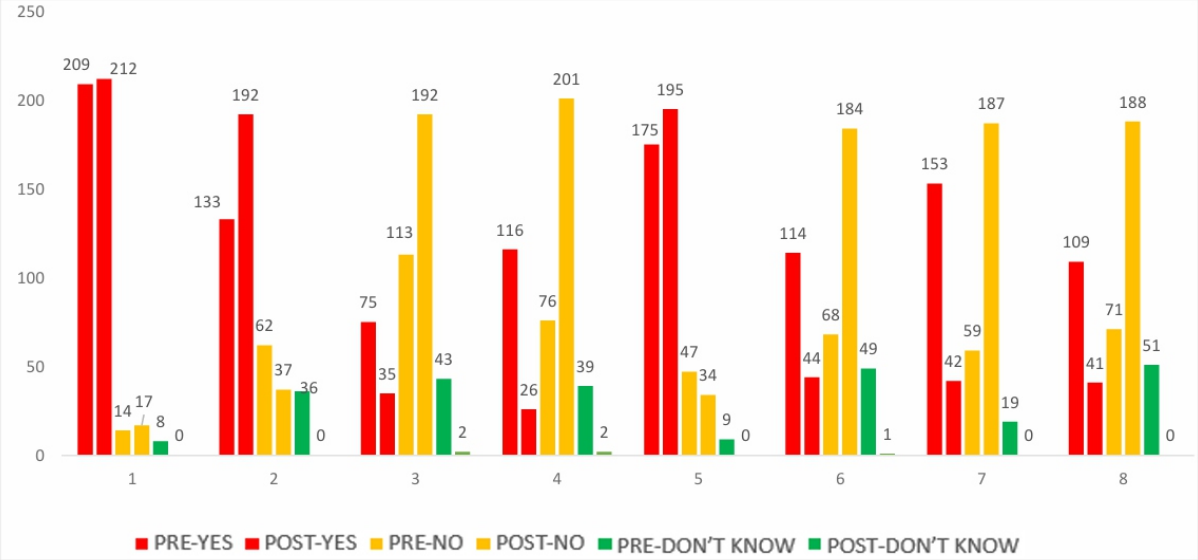

Fig. 1. Knowledge scores given by the pharmacists to questionnaires in the test group

Table 6. Details of attitude scores given by the pharmacists to questionnaires in the test group

Sl. No	Questionnaires	Pre-Intervention			Post-Intervention		
		Yes	No	Don't Know	Yes	No	Don't Know
1	Is a program to gather medications from pharmacies necessary, in your opinion?	218	10	3	229	0	0
	Percentage (%)	94.3	4.32	1.29	100	0	0
2	Do you have any suggestions to improve the awareness of consumers regarding the safe disposal of medicines?	148	41	42	203	26	0
	Percentage (%)	64.06	17.7	18.18	88.6	11.3	0
3	Do you agree that improper dispensing of expired and unused medicines can pose hazards to public safety?	187	39	5	204	25	0
	Percentage (%)	80.9	16.8	2.16	89.08	10.9	0
4	Is the development of antibiotic resistance a real possibility due to improperly discarded medications?	189	24	18	206	22	1
	Percentage (%)	81.8	10.3	7.79	89.9	9.60	0.43

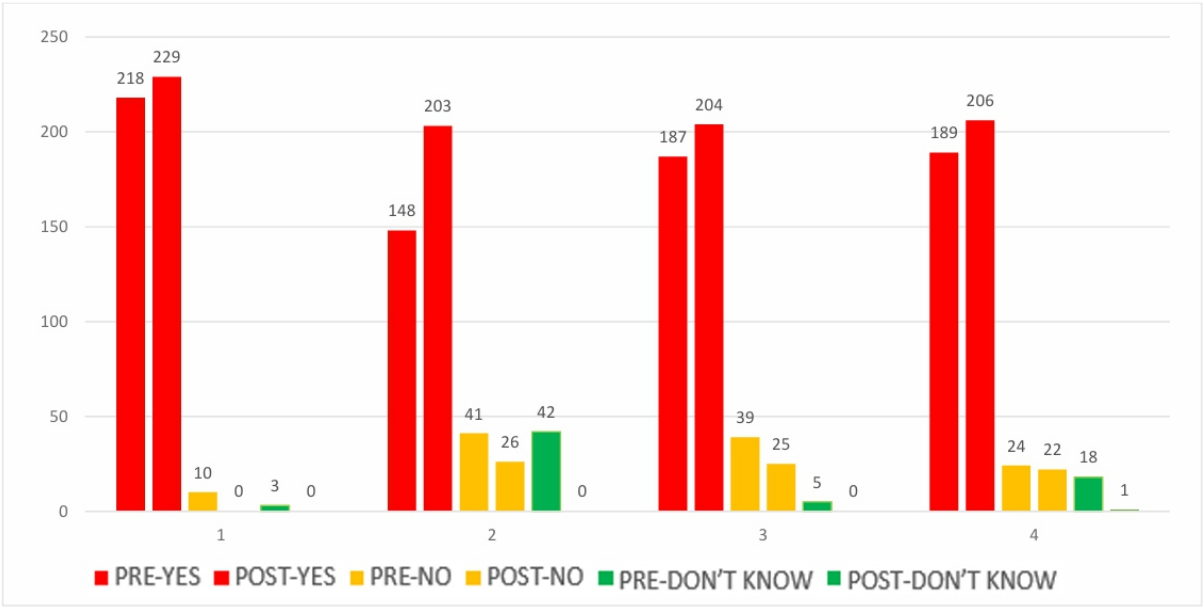

Fig. 2. Attitude scores given by the pharmacists to questionnaires in the test group

5. It was compelling to know, 175 (75.7%) of them, knew drugs can cause environmental pollution, 47 (20.3%) did not know about, 9 (3.87%) don't know anything about the drug causing environmental pollution in the Preintervention. In the Post-intervention, 195 (85.1%) knew drugs can cause environmental pollution, 34 (14.8%) did not know about it. This clearly states, that most of the pharmacists knows about the drugs can cause environmental pollution. The current study results were similar to Siva Shree Rajgopalan Suresh babu et.al. (2021)

6. Out of 231 pharmacists, 114 (49.3%) received information about how to dispose unused and unwanted medicines, 68 (29.4%) did not receive any information, 49 (21.2%) don't know about it. In the post intervention, 44 (19.2%) received information, 184 (80.3%) did not receive information about it, 1 (0.43%) don't know about it.

7. Out of 231 pharmacists, 153 (66.2%) dispose left over medicines monthly, 59 (25.5%) don't dispose of medicines monthly, 19 (8.22%) don't know about it. In the Post-intervention, 42 18.3% dispose left over medicines monthly, 187 (81.6%) don't dispose of medicines monthly. In the intervention, we got to know that, the pharmacists dispose of the medicines for every 2-3 months.

8. Out of 231 pharmacists, 109 (47.1%) know different guidelines for safe disposal of drugs, 71 (30.7%) said they did not know about it and 51 (22.07%) did not know anything about it. In the Post-intervention, 41 (17.9%) know different guidelines for disposal of drugs, 188 (82.09%) did not now different guidelines, Table 5.

1. In the Pre-Intervention, out of 231, 218 (94.3%) agreed that, there is a need for a program to collect medicines from pharmacy, 10 (4.32%) said that there is no need for a program to collect medicines from

pharmacy and 3 (1.29%) did not agree with anything. In Post-Intervention, out of 229, everyone agreed that, there is a need for a program to collect medicines from pharmacy. This signifies, that all pharmacists are ready to collect the medicines from the pharmacy.

2. In Pre-Intervention, out of 231, 148 (64.06%) had suggestions to improve awareness of consumers regarding safe disposal of medicines, 41 (17.7%) did not have any suggestions, 42 (18.18%) did not know anything about it. In PostIntervention, out of 229, 203 (88.6%) had suggestions to improve awareness of consumers regarding safe disposal of medicines, 26 (11.3%) did not have any suggestions. This signifies that after educating the pharmacists about the need of awareness, suggestions. they had multiple

3. In Pre-Intervention, out of 231, 187 (80.9%) agreed that improper dispensing of expired and unused medicines can pose hazards to public safety, 39 (16.8%) disagreed that improper dispensing do not pose any hazards and 5 (2.16%) did not know about it. In Post-Intervention, out of 229, 204 (89.08%) agreed that improper dispensing can pose hazards, 25 (10.9%) disagreed that improper disposing do not pose any hazards. This shows that, after education pharmacists understood that improper dispensing of unused and expired medicines can pose hazards to public safety. The current study results were similar to Binu K.M et.al. (2022).

4. In Pre-Intervention, out of 231, 189 (81.8%) agreed that unsafe disposed drugs can lead to antibiotic resistance, 24 (10.3%) disagreed that unsafe disposed drugs can lead to antibiotic resistance, 18 (7.79%) did not had anything to say about it. In Post-Intervention, out of 229, 206 (89.9%) agreed that unsafe disposed dugs can lead to antibiotic resistance, 22 (9.60%) disagreed and 1 (0.43%) did not say anything about it. This signifies that pharmacists knew that unsafe disposed drugs can lead to antibiotic resistance, Table 6.

Table 7. Details of practice scores given by the pharmacists to questionnaires in the test group

Sl. No	Questionnaires	Pre-Intervention			Post-Intervention		
		Yes	No	Don't Know	Yes	No	Don't Know
1	Do you know about national take-back programs in other countries for the return of medications from pharmacies?	147	35	49	20	208	1
	Percentage (%)	63.6	15.15	21.2	8.73	90.82	0.43
2	Do you agree with the opinion of having your pharmacy take back leftover or expired medicines?	136	65	30	216	12	1
	Percentage (%)	58.8	28.1	12.9	94.32	5.24	0.43
3	If a patient brings to you some leftover medicines or expired medications for safe disposal. Would you accept it?	120	57	54	38	191	0
	Percentage (%)	51.94	24.6	23.3	16.59	83.40	0
4	Do you agree that it is your professional responsibility to be concerned about the safety of humans and other living species on the earth?	177	39	15	205	23	1
	Percentage (%)	76.6	16.8	6.49	89.51	10.04	0.43
5	Are there any medication safety posters up in your pharmacy?	153	53	25	123	105	1
	Percentage (%)	66.2	22.9	10.8	53.711	45.85	0.43
6	If there is a course on the take-back program, would you be interested in taking part in it?	180	40	11	125	104	0
	Percentage (%)	77.9	17.3	4.76	54.58	45.41	0

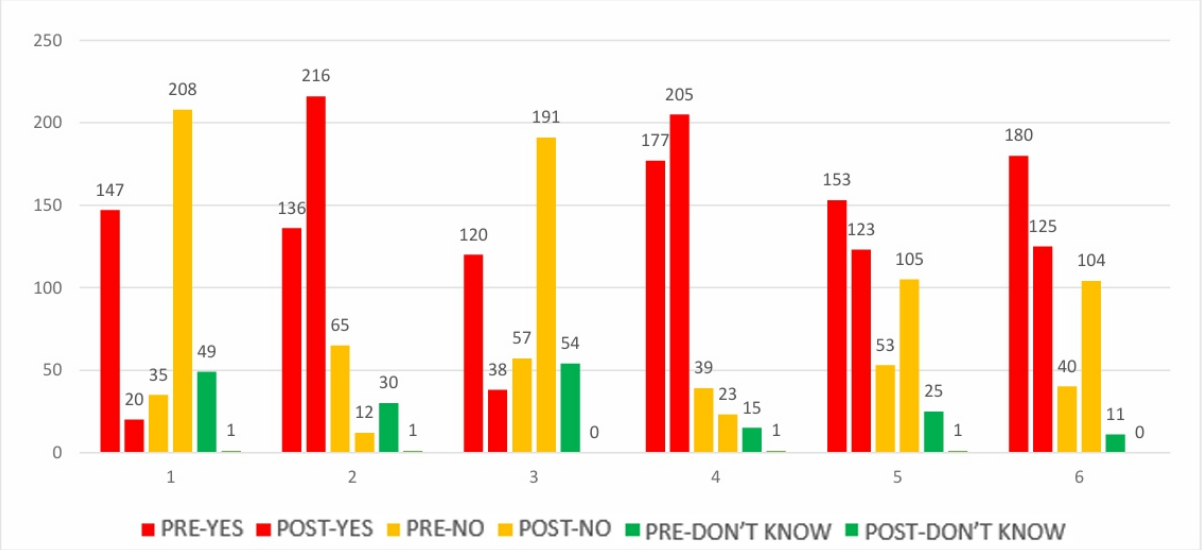

Fig. 3. Practice scores given by the pharmacists to questionnaires in the test group

1. In Pre-Intervention, out of 231, 147 (63.6%) knows, about the take back programmes in other countries for return of medications from pharmacies, 35 (15.15%) does not know about the take back programmes, 49 (21.2%) did not know anything about it. In PostIntervention, out of 229, 20 knows, about the take back programmes and 208 (90.82%) does not know about the take back programmes, 1 (0.43%) did not know anything about it. This signifies that pharmacists were not aware of the take back programmes in the other countries.

2. In Pre-Intervention, out of 231, 136 (58.8%) agreed with the opinion of having take back of left over or expired medicines in their pharmacies, 65 (28.1%) disagreed with the opinion, 30 (12.9%) did not had anything to say. In Post-Intervention, out of 229, 216 (94.32%) agreed with the opinion, 12 (5.24%) disagreed with the opinion, 1 (0.43%) still had no idea about it. This signifies that pharmacists were ready to accept the left over or expired medicines in their pharmacies.

3. In Pre-Intervention, out of 231, 120 (51.94%) said that they will accept, if any patient gets some left over or expired medications for safe disposal, 57 (24.6%) said they will not accept, 54 (23.3%) had no idea about it. In Post-Intervention, out of 229, 38 (16.59%) said that they will accept, 191 (83.40%) said they will not accept it. This shows that the pharmacists are not willing to accept the left over or expired medicines from patients for safe disposal.

4. In Pre-Intervention, out of 231, 177 (76.6%) agreed that, it is professional responsibility to be concerned about the safety towards human and other living species on the earth, 39 (16.8%) disagreed with it, 15 (6.49%) said that, they don't know about it. In PostIntervention, out of 229, 205 (89.51%) agreed that, it is professional responsibility, 23 (10.04%) disagreed to it, 1 (0.43%) said they don't know about it. This shows that the pharmacists were concerned about the safety of humans and other living species.

5. In Pre-Intervention, out of 231, 153 (66.2%) said, they have posters about drug safety in their pharmacies, 53 (22.9%) said, they don't have any posters about drug safety, 25 (10.8%) said, they don't know about drug safety posters. In Post-Intervention, out of 229, 123 (53.41%) said, they have posters about it, 105 (45.8%) said, they don't have any posters about it, 1 (0.43%) said, that they don't know about it. This shows that most of the pharmacists, did not display posters about drug safety in their pharmacies.

6. In Pre-Intervention, out of 231, 180 (77.9%) agreed to participate in a educational course on take back program, 40 (17.3%) disagreed to participate, 11 (4.76%) said they don't know about it. In Post-Intervention, out of 229, 125 (54.58%) agreed to participate, 104 (45.41%) disagreed. This shows that, most of the pharmacists agreed to participate in the take back program, Table 7.

• In the Control group, we had 230 pharmacists in the pre-intervention and in the post- intervention we had 227, 3 dropouts were seen in the control group.

1. In Kalaburagi city, out of 230 pharmacists about 204 (88.69%) of the pharmacists check the expiry date of the medicines before purchasing, 22 (9.56%) do not check the expiry date of the medicines and about 4 (1.73%) do not know about it, in Pre-intervention. In the Post-intervention, there were three dropouts, out of 227 pharmacists, about 134 (59.03%) check the expiry date of the medicines before purchasing, 90 (39.64%) did not check the expiry date, 3 (1.32%) do not know about it. 2. Out of 230 pharmacists, In Pre- intervention, 126 (54.78%) knew how to dispose of nearly expired medicines, 77 (33.47%) did not know how to dispose of the nearly expired medicines and 27 (11.73%) do not know about the disposal of nearly expired medicines.

Table 8. Details of knowledge scores given by the pharmacists to questionnaires in the control group

Sl. No	Questionnaires	Pre-Intervention			Post-Intervention		
		Yes	No	Don't Know	Yes	No	Don't Know
1	Do you check the expiry date of the medicines before purchasing?	204	22	4	134	90	3
	Percentage (%)	88.69	9.56	1.73	59.03	39.64	1.32
2	Do you know the procedure for disposing of nearly expired medicines?	126	77	27	99	127	1
	Percentage (%)	54.78	33.47	11.73	43.61	55.94	0.44
3	Are there any medications in your pharmacy that you aren't using right now?	93	111	26	108	115	4
	Percentage (%)	40.43	48.26	11.30	47.57	50.66	1.76
4	Do you know the average shelf life of the medicines?	115	91	25	121	103	3
	Percentage (%)	50	39.56	10.86	53.30	45.37	1.32
5	Do you know drugs can cause environmental pollution?	166	51	13	115	109	3
	Percentage (%)	72.17	22.17	5.65	50.66	48.01	1.32
6	Have you ever gotten instructions on what to do with old or unwanted medications?	111	83	36	122	102	3
	Percentage (%)	48.26	36.08	15.65	53.74	44.93	1.32
7	Do you dispose of leftover medicines monthly?	146	71	13	147	77	3
	Percentage (%)	63.47	30.86	5.65	64.75	33.92	1.32
8	Do you know different guidelines for the safe disposal of drugs?	114	80	36	174	77	3
	Percentage (%)	49.56	34.78	15.65	64.75	33.92	1.32

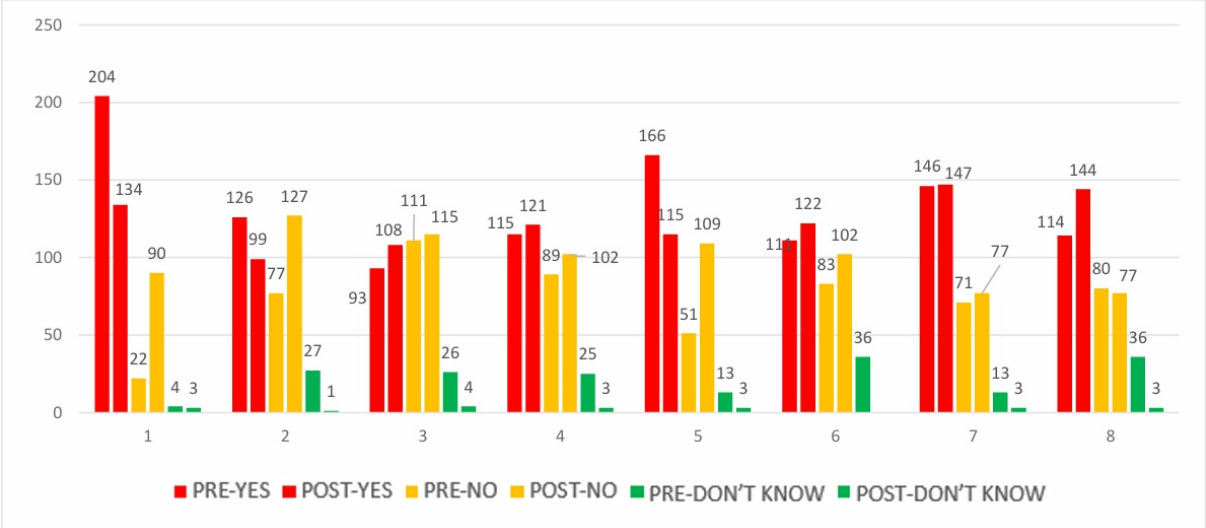

Fig. 4. Knowledge scores given by the pharmacists to questionnaires in the control group

In the Post-intervention, out of 227, 99 (43.61%) knew how to dispose of nearly expired medicines, 127 (55.94%) did not know how to dispose of the nearly expired medicines and 1 (0.44%) do not know about it.

3. In Pre-intervention, 93 (40.43%) currently had unused medications stored at their pharmacies, 111 (48.26%) did not store any unused medications stored at their pharmacies and 26 (11.30%) do not know whether they stored any unused medications at their pharmacies. In Postintervention, 108 (47.57%) currently had unused medications stored at their pharmacies, 115 (50.66%) did not store any unused medications stored at their pharmacies and 4 (1.76%) do not know whether they stored any unused medications at their medications.

4. While interacting with the pharmacists, out of 230 in Pre-intervention, 115 (50%) said they knew about average shelf life of the medicines, 91 (39.56%) did not know about the average shelf life, 13 (10.86%) do not know about it. In the postintervention, 121 (53.30%) knew about average shelf life of the medicines, 109 (10.3%) did not know about the average shelf life and 3 (1.32%) knew anything about it.

5. Out of 230 pharmacies, 166 (72.17%) of them, knew drugs can cause environmental pollution, 83 (22.17%) did not know about, 36 (5.65%) do not know anything about the drug causing environmental pollution in the Preintervention. In the Post-intervention, 115 (50.66%) knew drugs can cause environmental pollution, 109 (48.01%) did not know about it, 3 (1.32%) do not know anything about it.

6. Out of 230 pharmacists, 111 (48.26%) received information about how to dispose unused and unwanted medicines, 83 (36.08%) did not receive any information, 36 (15.65%) do not know about it. In the post intervention, 122 (53.74%) received information, 102 (44.93%) did not receive information

about it, 3 (1.32%) do not know about it.

7. Out of 230 pharmacists, 146 (63.47%) dispose left over medicines monthly, 71 (30.86%) do not dispose of medicines monthly, 13 (5.65%) do not know about it. In the Post-intervention, 147 (64.75%) dispose left over medicines monthly, 77 (33.92%) do not dispose of medicines monthly, 3 (1.32%) do not know anything about it. In the intervention, we got to know that, the pharmacists dispose of the medicines for every 2-3 months.

8. Out of 230 pharmacists, 114 (49.56%) know different guidelines for safe disposal of drugs, 80 (34.78%) said they did not know about it and 36 (15.65%) did not know anything about it. In the Postintervention, 174 (64.75%) aware of different guidelines for disposal of drugs, 77 (33.92%) did not now different guidelines, 3 (1.32%) do not know anything about it. The current study results were similar to Siva Shree Rajgopalan Suresh Babu et.al. (2021), Table 8.

1. In the Pre-Intervention, out of 230, 211 (91.73%) agreed that, there is a need for a program to collect medicines from pharmacy, 18 (7.83%) said that there is no need for a program to collect medicines from pharmacy and 1 (0.43%) did not agree with anything. In Post-Intervention, out of 227, 18 (7.92%) agreed that, there is a need for a program to collect medicines from pharmacy, 209 (92.07%) disagreed with it.

2. In Pre-Intervention, out of 230, 143 (62.17%) had suggestions to improve awareness of consumers regarding safe disposal of medicines, 50 (21.73%) did not have any suggestions, 37(16.08%) did not know anything about it. In PostIntervention, out of 227, 116 (51.10%) had suggestions to improve awareness of consumers regarding safe disposal of medicines, 109 (48.01%) did not have any suggestions, 2 (0.88%) do not know about it.

3. In Pre-Intervention, out of 230, 179 (77.82%) agreed that improper dispensing of expired and unused medicines can pose hazards to public safety, 38 (16.52%) disagreed that improper dispensing do not pose any hazards and 13 (5.65%) did not know about it. In Post-Intervention, out of 227, 107 (47.13%) agreed that improper dispensing can pose hazards, 119 (52.42%) not agreed that improper disposing do not pose any hazards, 1 (0.44%) don't know about it.

Table 9. Details of attitude scores given by the pharmacists to questionnaires in the control group

Sl. No	Questionnaires	Pre-Intervention			Post-Intervention		
		Yes	No	Don't Know	Yes	No	Don't Know
1	What is your opinion on the need of a program to retrieve medications from pharmacies?	211	18	1	18	209	0
	Percentage (%)	91.73	7.82	0.43	7.92	92.07	0
2	Do you have any suggestions to improve the awareness of consumers regarding the safe disposal of medicines?	143	50	37	116	109	2
	Percentage (%)	62.17	21.73	16.08	51.10	48.01	0.88
3	Do you agree that improper dispensing of expired and unused medicines can pose hazards to public safety?	179	38	13	107	119	1
	Percentage (%)	77.82	16.52	5.65	47.13	52.42	0.44
4	In your opinion, can antibiotic resistance be caused by improperly disposed of drugs?	177	27	26	109	117	1
	Percentage (%)	76.95	11.73	11.30	48.01	51.54	0.44

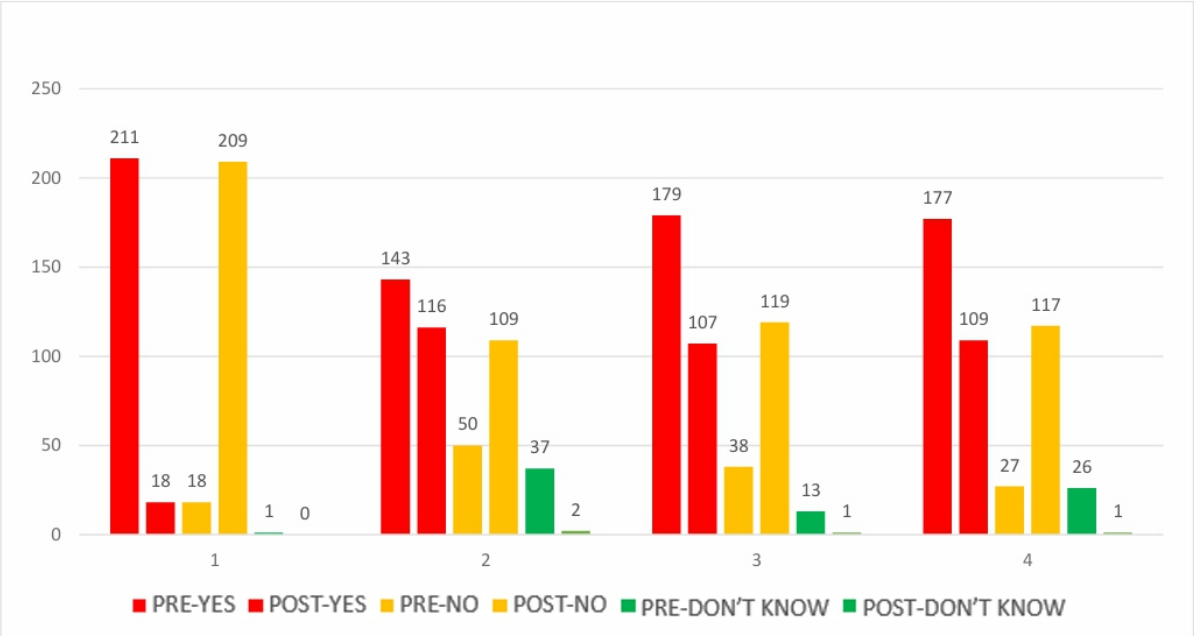

Fig. 5. Attitude scores given by the pharmacists to questionnaires in the control group

Table 10. Details of practice scores given by the pharmacists to questionnaires in the control group

Sl. No	Questionnaires	Pre-Intervention			Post-Intervention		
		Yes	No	Don't Know	Yes	No	Don't Know
1	Do you know about national take-back programs in other countries for the return of medications from pharmacies?	160	43	27	164	53	10
	Percentage (%)	69.56	18.69	11.73	72.24	23.34	4.40
2	Do you agree with the opinion of having your pharmacy take back leftover or expired medicines?	163	55	12	99	126	2
	Percentage (%)	70.86	23.91	5.21	43.61	55.50	0.88
3	If a patient brings to you some leftover medicines or expired medications for safe disposal. Would you accept it?	129	77	24	138	85	4
	Percentage (%)	56.08	33.47	10.43	60.79	37.44	1.76
4	Do you agree that it is your professional responsibility to be concerned about the safety of humans and other living species on the earth?	165	51	14	107	119	1
	Percentage (%)	71.73	22.17	6.08	47.13	52.42	0.44
5	Are there any medication safety posters displayed in your pharmacy?	159	60	11	139	86	2
	Percentage (%)	69.13	26.08	4.78	61.23	37.88	0.88
6	If there is a course on the take-back program, would you be interested in taking part in it?	170	42	18	128	92	7
	Percentage (%)	73.91	18.26	7.82	56.38	40.52	3.08

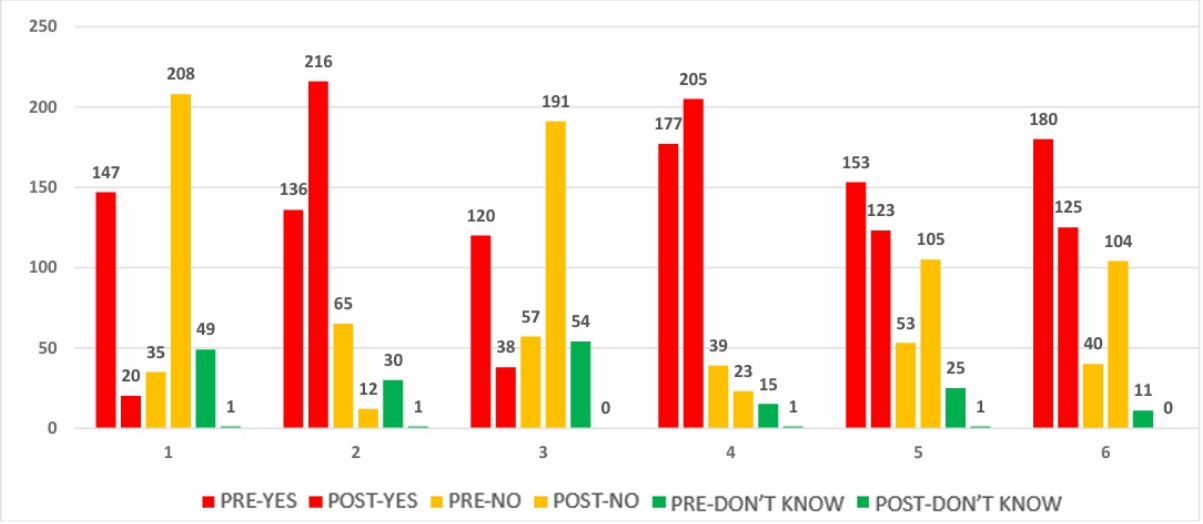

Fig. 6. Practice scores given by the pharmacists to questionnaires in the control group

4. In Pre-Intervention, out of 230, 177 (76.95%) agreed that unsafe disposed drugs can lead to antibiotic resistance, 27 (11.73%) disagreed that unsafe disposed drugs can lead to antibiotic resistance, 26 (11.30%) did not had anything to say about it. In Post-Intervention, out of 227, 109 (48.01%) agreed that unsafe disposed dugs can lead to antibiotic resistance, 117 (51.54%) not agreed and 1 (0.44%) did not say anything about it. The current study results were similar to Siva Shree Rajgopalan Suresh Babu et.al. (2021), Table 9.

1. In Pre-Intervention, out of 230, 160 (69.56%) knows, about the take back programs in other countries for return of medications from pharmacies, 43 (18.69%) does not know about the take back programs, 27 (11.73%) did not know anything about it. In Post-Intervention, out of 227, 164 (72.24%) knows, about the take back programs and 43 (18.69%) does not know about the take back programs, 27 (11.73%) did not know anything about it.
2. In Pre-Intervention, out of 230, 163 (70.86%) agreed with the opinion of having take back of left over or expired medicines in their pharmacies, 55 (23.91%) disagreed with the opinion, 12 (5.21%) did not had anything to say. In Post-Intervention, out of 227, 99 (43.61%) agreed with the opinion, 126 (55.50%) disagreed with the opinion, 2 (0.88%) still had no idea about it.
3. In Pre-Intervention, out of 230, 129 (56.08%) said that they will accept, if any patient gets some left over or expired medications for safe disposal, 77 (33.47%) said they will not accept, 24 (10.43%) had no idea about it. In Post-Intervention, out of 227, 138 (60.79%) said that they will accept, 85 (37.44%) said they will not accept it, 4 (1.76%) said they don't know about it.
4. In Pre-Intervention, out of 230, 165 (71.73%) agreed that, it is professional responsibility to be concerned about the safety towards human and other living species on the earth, 51 (22.17%) disagreed with it, 14 (6.08%) said that, they don't know about it.

In Post-Intervention, out of 227, 107 (47.13%) agreed that, it is professional responsibility, 119 (52.42%) disagreed to it, 1 (0.44%) said they don't know about it.

5. In Pre-Intervention, out of 230, 159 (69.13%) said, they have posters about drug safety in their pharmacies, 60 (26.08%) said, they don't have any posters about drug safety, 11 (4.78%) said, they don't know about drug safety posters.

In Post-Intervention, out of 227, 139 (61.23%) said, they have posters about it, 86 (37.88%) said, they don't have any posters about it, 2 (0.44%) said, that they don't know about it.

6. In Pre-Intervention, out of 230, 170 (73.91%) agreed to participate in an educational course on take back program, 42 (18.26%) disagreed to participate, 18 (7.82%) said they do not know about it. In Post-Intervention, out of 227, 128 (56.38%) agreed to participate, 92 (40.52%) disagreed, 7 (3.08%) do not know about it, Table 10.

4. CONCLUSION

• The current KAP research of Kalaburagi city's chosen community pharmacists focuses on their understanding of, and approach to, proper medication disposal for unused and expired medications.

• A serious problem that need attention is the lack of knowledge about the consequences of incorrectly disposing of prescription items.

• When it comes to collecting and disposing of unneeded medications, the present procedures and techniques used by pharmacists are not up to par.

• The concerns are brought to light by highlighting the role of pharmacists.

• A combination of policies and initiatives may safeguard people and the environment by reducing potential dangers.

• Our research shows that in Kalaburagi city, community pharmacists outperform their government counterparts when and it hospital comes to understanding the need of safe medication disposal and taking measures to avoid it.

• We educated them on how to properly dispose of medications, unneeded and expired administered surveys, distributed pamphlets, and showed them movies and clips as part of our baseline research.

• Additionally, we find that pharmaceutical compounds are a class of new environmental pollutants in our research. Veterinary health is crucial since even minute concentrations pose a significant threat because to their persistent release into the environment and the damage they do to both people and ecosystems.

• Prior to the release of every new medication, it is now standard practice to conduct an environmental risk assessment. Pharmaceutical companies and universities should do research on eco-pharmacovigilance, and there should be rules and regulations about ecopharmacovigilance rational medicine, drug tack-back programs, strengthened policies, and guidelines. The field known as "Eco-Pharmacovigilance" emerged as a result of this.

• With the country's pharmaceutical sector and medicine use on the rise, India has a duty to its own people, environment, and global ecosystem.

5. LIMITATIONS

1. Lack of knowledge regarding the safe disposal of medicines among some community pharmacies as well as among the general public.
2. Lack of government programs such as medicine take-back programs.
3. Time management problems, language, and communication barriers
4. Availability of participants and willingness to participate in the study.

6. FUTURE PERSPECTIVES

1. Based on the findings of the aforementioned research, it is clear that a worldwide system is required for the mandatory collecting of families' unused and expired medications.
2. In addition to the system, there has to be an awareness campaign to teach the public about safe disposal methods and the negative outcomes that might result from individuals not following these protocols.
3. Pharmacies should be educated regarding safe disposal of medicines and pharmaceutical products.
4. Drug take-back and other educational initiatives should be encouraged in our country.
5. Keeping a global EPV perspective.
6. A number of mass media platforms should be actively engaged in raising awareness.
7. It is important to establish appropriate channels that include drug regulatory agencies, population control boards, nongovernmental organizations (NGOs), and civil society.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Mindfulness-based Therapies and Cancer-related Fatigue: A Narrative Review

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ABSTRACT

Globally, the prevalence of cancer is steadily increasing, making it the second most common cause of death from non-communicable diseases, after cardiovascular disorders. It represents the highest rates of morbidity and mortality, and its prevalence continues to rise. Despite significant advancements in treatments, most cancer therapies are associated with both immediate and long term side effects, including nausea, fatigue, appetite loss, hair loss, pain, and others. One of the most common and debilitating symptoms is Cancer-Related Fatigue (CRF). According to the European Association of Palliative Care, fatigue is "a subjective feeling of tiredness, weakness, or lack of energy." CRF can develop at any stage of the illness and may persist for years after treatment. The primary objective of this review is to explore the impact of mindfulness-based therapies in managing CRF. Integrative oncology, combining conventional therapies with evidencebased Complementary and Alternative Medicine (CAM) practices, offers a holistic, patient-centered approach to CRF management. This includes mindfulness-based and biobehavioural therapies, such as yoga and meditation. This review aims to examine the research on the successful application of mindfulness techniques to effectively address CRF, offering insights for improving patient care and quality of life.

Keywords: Cancer-related fatigue; mindfulness; yoga.

1. INTRODUCTION

Cancer is the second most common cause of non-communicable disease-related mortality following cardiovascular disease (Shaji et al., 2023). Being one of the most feared chronic diseases, it also accounts for the highest rate of morbidity. Worldwide, several millions of individuals are diagnosed with cancer, and its incidence is still on the rise. A cancer diagnosis is a major life stressor that can negatively impact a person's physical, social, spiritual, and psychological well-being. Despite interesting advancements in the available treatment modalities, most of the cancer treatment regimens are associated with immediate and late side effects. Nausea, vomiting, fatigue, loss of appetite, changes in taste, dry mouth, hair loss, altered bowel habits, and pain are a few of them (Altun & Sonkaya, 2018).

Fatigue is very prevalent and is one of the most distressing symptoms that have a detrimental impact on the overall quality of life during all stages and facets of the cancer journey (Al Maqbali et al., 2021). It is described as "a subjective feeling of tiredness, weakness, or lack of level, which is not related to previous activities and cannot be entirely reduced by sleep (Bower, 2014). 90% of cancer patients report CRF during their active treatment and more than 50% of them report fatigue after the completion of the treatment. It may set in both as a consequence of cancer as well as a side effect of cancer treatment. CRF is not just a symptom of advanced cancer, it can arise at any stage of the disease and can last for years after the completion of the treatment regimen (Kirshbaum, 2010). As CRF directly impairs and hinders the overall quality of life in cancer survivors, effective management of CRF is vital to address the multifaceted impact of this symptom on cancer patient's physical, emotional, and social wellbeing. And it is crucial to assist patients in coping with this difficult aspect of cancer and its treatment. For the best management of CRF, a multimodal approach that involves both pharmaceutical and non-pharmacological interventions is frequently advocated. energy," according to the European Association of Palliative Care (EAPC) (Radbruch et al., 2008). One of the most debilitating symptoms cancer patients succumb to is fatigue.

A meta-analysis conducted by Mustian et al included the four most commonly recommended treatments for CRF including exercise,psychological intervention combined, and pharmacological intervention, and concluded that pharmacological interventions did not improve CRF to the same extent as nonpharmacological interventions (Mustian et al., 2017). It is crucial to intervene and to provide the best comprehensive management strategy with the combination of CAM system and with patient-centred, individually tailored holistic approach.

MBIs are evidence-based intervention for treating symptoms of cancer and its treatments, which cannot be effectively treated with the pharmacological interventions. Being Mindful- is to be aware of one’s thoughts, feelings, body sensations, and surroundings in the present moment (Baer et al., 2019). With a salutogenic, health-promoting focus that encourages and promotes mindfulness, which subsequently helps one to become aware of his current moment, it also complements conventional medicine. Additionally, it aids in actively setting aside anxieties from one's thoughts, which lessens stress and promotes relaxation and simultaneous mental and physical recovery. MBIs teach participants to pay attention to present-moment experiences in a compassionate and nonjudgmental manner (Shapero et al., 2018).

Mindfulness focuses on accepting the current moment without judgement. Cancer patients can utilise mindfulness to manage with their challenges, cultivating acceptance and lowering the mental and

emotional energy used on opposing or struggling with their situation. MBI has definitive effect on anxiety, depression, pain, loneliness, and sleep disturbance, and that in turn will help to relieve fatigue related to cancer such as emotional distress, sleep disorder, activity level, malnutrition, pain, anaemia and non-cancer commodities.

A study conducted by Ikeuchi K et al., concluded that - mindfulness, has a direct effect on fatigue,and also indirectly mitigates anxiety, depression, pain, sense of isolation, and sleep dysfunction and hence will alleviate the symptom of fatigue among cancer patients (Ikeuchi et al., 2020).

1.1 Aim and Objective of the Current Review

This review is aimed at mapping the available literature and to provide thorough thought on the significance of Mindfulness-Based Interventions (MBIs) on cancer-related fatigue (CRF).

2. METHODS

2.1 Literature Research

This review consists of a literature search at NCBI PubMed, Cochrane, and EMBASE using keywords like mindfulness-based interventions, mind-body intervention, cancer, and oncology. For a broader range of searches, there was inclusion of terms like Yoga, meditation, mindfulness-based stress reduction, and mindfulness meditation. Full-text copies of all studies of possible relevance were obtained. A manual search of reference lists of all approved papers was conducted for additional information, ensuring the inclusion of relevant articles identified through cross-references.

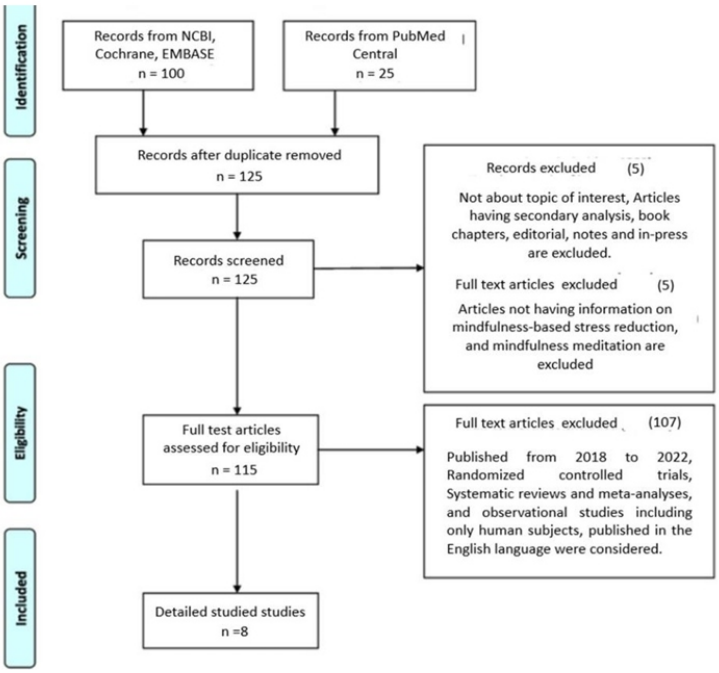

Fig. 1. Flow Chart of identification and screening of studies via Database search

Table 1. Mindfulness-based interventions given to cancer patients, published in 2018–2022

S. No.	Author	Study Design	Sample size	Methodology	Result	Conclusion
1	(Haller et al., 2021)	An Observational Study	n = 57	In addition to standard care, female breast cancer patients received 66 hours of personalized mind- body-medicine group therapy. Mindfulness training, yoga, moderate exercise, diet, complementary self-help tactics, cognitive restructuring, and acupuncture were the part of the program.	Global EORT quality of life was improved among the patients. Stress, anxiety and depression were also found to be significantly reduced. Noticeable changes were also observed in the fatigue levels experienced by the patients.	Breast cancer patients benefit from an integrative mind-body medicine group program during chemotherapy in terms of quality of life and psychological symptoms.
2	(Zhang et al., 2019)	A systematic review and meta-analysis	NA (N= 1082)	A systematic search in many electronic databases were done using appropriate keywords to arrive at the trials examining the effects of Mindfulness-Based Stress Reduction (MBSR) on breast cancer patients.	7 studies reported that MBSR had a positive effect on fatigue among patients with breast cancer.	MBSR can be offered to breast cancer patients as a supplemental or adjunctive therapy.
3	(Johns et al., 2021)	A systematic review and meta-analysis of randomized controlled trials	N = 2239	A thorough search in multiple electronic databases was conducted using appropriate keywords to find randomized controlled studies assessing the efficacy of Mindfulness-Based Interventions (MBIs) in improving fatigue related outcomes in adult cancer survivors.	MBIs significantly reduced fatigue compared to controls at the post- intervention.	MBIs show promise in improving fatigue and vitality/vigor in cancer survivors.
4	(McCloy et al., 2022)	A systematic review and meta-analysis of randomised control trials	N = 2326	Five electronic databases and two trial registrations were searched for randomised control trials that investigated the effects of mindfulness on cancer-related fatigue (CRF) and psychological well-being in female cancer patients.	Mindfulness significantly improved CRF, depression and anxiety among female patients with cancer.	Mindfulness appears to be useful in lowering CRF in female cancer survivors.
5	(Ng et al., 2021)	Randomized controlled trial	n = 80	The study recruited patients with hematological malignancies who had a fatigue. The intervention group received standard care plus a 30- minute guided mindful breathing session, while the control group received standard care.	The interventional group exhibited lower fatigue scores on both the Edmonton Symptom Assessment System (ESAS) and the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scales at the 30th minute.	A single 30- minute session of mindful breathing is beneficial in lowering fatigue in haematological cancer patients and can be regarded a valuable addition to existing treatments.
6	(Liu et al., 2021)	Randomized controlled trial	n = 120	Patients with Differentiated Thyroid Cancer were randomly assigned to the Mindfulness-Based Stress Reduction (MBSR) intervention group or the usual care group. The MBSR group received an 8- week MBSR programme that began 8 weeks before radioactive iodine therapy (RIT).	Patients in the MBSR group improved significantly more in terms of emotional function, fatigue, general quality of life, depression, and anxiety.	An 8-week MBSR program can significantly improve a wide range of scales in health-related QoL and can mitigate depression and anxiety among differentiated thyroid cancer (DTC) receiving RIT.

S. No.	Author	Study Design	Sample size	Methodology	Result	Conclusion
7	(Sheikhzadeh et al., 2021)	Randomized controlled trial	n = 60	Patients diagnosed with cancer were randomly allocated to 3 groups, namely Mindfulness-Based Cognitive Therapy (MBCT), Cognitive Behavioral Therapy (CBT) and wait-list group (WLG). 8 weeks of intervention was given.	There was a significant reduction in depression, anxiety, and fatigue levels in the CBT and MBCT groups.	CBT and MBCT could be considered a good addition to pharmacological treatment for cancer patients with concomitant psychosocial symptoms.
8	(Gok Metin et al., 2019)	An assessor blinded, three- arm, randomized controlled trial	n = 92	Participants from three groups were randomly assigned to Progressive Muscle Relaxation (PMR), Mindful Meditation (MM) and control groups. The interventions were given for 12 weeks and control group received a single time attention-matched education for 15- min on breast cancer before the start of their chemotherapy regimen.	At weeks 12 And 14, the PMR and MM groups had significantly lower Brief Fatigue Inventory (BFI) scores as compared to the Control Group.	PMR and MM are effective therapies that, when combined with chemotherapy, will be beneficial for reducing fatigue among patients with breast cancer.

2.2 Selection of the Studies

To include in this review, articles signifying the efficacy of mindfulness-based interventions in the management of cancer-related fatigue, published from 2018 to 2022, Randomized controlled trials, Systematic reviews and meta-analyses, and observational studies including only human subjects, published in the English language were considered (Fig. 1). Screening was performed for titles and abstracts by two independent review authors, potentially eligible citations were retrieved for full-text review. A third review author checked the excluded records. Abstracts, editorials, conference proceedings, clinical trial registrations, and grey literature were excluded (Table 1).

3. RESULTS

A total of 115 articles were identified through the electronic database search. Title and abstract screening were performed for all the relevant articles. After the application of inclusion and exclusion criteria, 8 studies were found appropriate for this review. In examining the diverse body of literature related to the efficacy of mindfulness-based interventions on cancer related fatigue, several prominent findings were noted, reflecting both the depth and breadth of research in this field. Numerous studies have been taken up by enthusiastic researchers to explore the benefits of mindfulness-based interventions among cancer patients. The synthesis of evidence revealed a compelling linkage between MBIs and CRF, shedding light on the intricate interplay between these essential components in cancer care. This integrative approach highlights the complexity of the subject matter and lays the groundwork for a more nuanced understanding. As we delve deeper into the literature, a notable pattern emerged regarding the benefits of MBIs in the management of CRF.

4. DISCUSSION

According to the literature, fatigue can be caused by the interaction of several psycho-physiological processes. Further, evidence (Liu X et al.,) suggests that cancer and its treatments activate the immune system by triggering the production of pro-inflammatory cytokines, resulting inperipheral inflammation; these events subsequently alter the glucocorticoid hormone response and cause mitochondrial dysfunction. A study on mindfulness interventions in cancer patients show that mindfulness can boost the function of anti-inflammatory glucocorticoid receptors in leucocytes (Carlson et al., 2019). According to the previously published evidence (Kim et al., 2021), the practice of mindfulness can guide participants purposefully pay attention to the present moment and non-judgmentally monitor the unfolding of experiences moment by moment, and therefore having a profound benefit via the mind-body connection. It guides individuals to focus on their bodily sensations and acknowledge any discomfort without interpretation, elaboration, or evaluation. This enables people to recognise, accept, and disengage from unpleasant bodily sensations and dysfunctional thinking processes. By this, an individual will also learn strategies to combat reactive avoidance behaviour and ruminative thought patterns that are akin to the development and relapse of anxiety and depression and thereby helps to lessen the overall symptom burden of fatigue.

Johns et al. (Johns et al., 2021) conducted a pilot study to examine the efficacy of mindfulnessbased stress reduction (MBSR) for CRF and related symptoms in a sample of 35 cancer survivors. They were allocated to either a 7-week MBSR intervention or a wait-list control group. The study found that mindfulness-based stress reduction is a promising treatment for CRF and associated symptoms. A study conducted by (Zetzl et al., 2021) also found that weekly reminder e-mails can positively influence cancer patients to establish a regular Yoga practice at home and they will have improvement in their general and emotional fatigue. This can also be used as a strategy for the continued practice of MBIs to get the desired physiological benefits. Two prominent meta-analyses have provided strong evidence supporting the efficacy of Mindfulness-Based Stress Reduction (MBSR) in managing CRF. A meta-analysis by Xie et al., showed that MBSR was a successful intervention in reducing the severity of CRF, with notable improvements in patients' levels of fatigue and general well-being (Xie C, Dong B, Wang L, et al., 2020). The comprehensive benefits of mindfulness for cancer patients were also

demonstrated by He et al., who conducted a systematic review and meta-analysis and discovered that MBSR interventions not only significantly reduced CRF but also improved psychological distress (He J, Hou JH, Qi J, et al., 2020). These findings reinforce the value of integrating mindfulness practices, into holistic treatment plans for individuals experiencing CRF, offering a promising non-pharmacological approach to support cancer patients' quality of life.

Even when the world was hit by COVID-19, Internet-Based Mindfulness-Based Stress Reduction (iMBSR) program was found beneficial for patients with Breast Cancer. A study conducted by Chuanyuan Kang and his coworkers concluded that, an 8 weeks of iMBSR was efficacious in reducing the psychological symptoms and in improving quality of life (Kang et al., 2021). It is also been found that MBIs given to family care givers of cancer patients has the potential to enhance the overall wellbeing and can reduce the burden on family care givers. And this in turn can help those family care givers to take more care of the cancer patient (Al Daken & Ahmad, 2018). al. In a qualitative study, Fernanda F. Zimmermann et concluded that, mindfulness-based the intervention like Coping with Cancer Mindfully can provide psychological and emotional support to patients with (Zimmermann et al., 2020). advanced cancer A Single-Blinded Randomized Controlled Trial conducted by Yildirim and his co-workers concluded that a 10-day mindfulness-based stress reduction programme combined with music therapy had considerably reduced stress and depression levels and also improved overall psychological well-being scores (Yildirim et al., 2024). Certainly, based on the available evidence and research findings, it can be concluded that MBIs show promise in effectively reducing CRF. Numerous studies, have suggested that incorporating mindfulness practices, such as meditation and mindful awareness, into the treatment plans of cancer patients can lead to significant improvements in fatigue levels (Xie C et al., & Johns SA et al.,). These interventions not only address the physical aspects of fatigue but also contribute to enhancing overall well being and quality of life for individuals undergoing cancer treatment.

Despite the richness of relevant insights, it is necessary to recognize the limitations of the studies addressed. It is crucial to recognize the heterogeneity of study designs, mindfulness interventions, and cancer populations found in the reviewed literature. Through a careful examination of the evidence presented in the reviewed articles, it becomes evident that there is a need for continued exploration and refinement of certain concepts, methodologies, and gaps in the existing literature. In future studies, standardization and rigorous methodology will boost the validity of findings and make it easier to identify specific characteristics that contribute to the success of mindfulness-based therapies. Additionally, the majority of studies predominantly focused only on mindfulnessbased stress reduction, raising questions about the broader applicability of the observed patterns.

The insights gained from this review contributes to the existing body of literature, provides a foundation for scholars, and practitioners to consider MBIs as a part of CRF management protocols. As the landscape of the topic evolves, this narrative review serves as a valuable resource for those seeking to navigate the effectiveness of MBIs in CRF management.

Although further research is needed to fully understand the mechanisms and long-term effects, the existing body of evidence supports the potential benefits of MBIs in alleviating CRF. Integrating these practices into comprehensive cancer care approaches may offer a valuable and holistic means of improving the overall health and resilience of cancer patients. Further many protocols must be conducted with RCTs and other standards to validate the beneficial influences of mindfulness-based interventions on cancer related fatigue. A more refined understanding of beneficial effects of MBIs, could inform more effective strategies for the management of CRF. The theoretical contributions of this review can encourage scholars to explore novel pathway in future research.

5. CONCLUSION

The evidence presented in this narrative review suggests that mindfulness-based interventions(MBIs) offer potential as a supportive approach for managing CRF. However, it is crucial to highlight that while MBIs show promise, they should be considered as part of a comprehensive, integrative approach that combines both conventional cancer treatments and complementary practices. The current body of evidence supports the inclusion of MBIs alongside conventional therapies, but more research, particularly with RCTs, is needed to validate their long-term effects and refine methodologies. Future studies should aim to standardize approaches and explore the broader applicability of MBIs in various cancer populations. The integration of MBIs into conventional treatment protocols could provide a more holistic and patient-centered care model, improving the overall health, resilience, and quality of life of cancer patients. As the field continues to evolve, ongoing investigation will be critical to understanding the full potential of MBIs in CRF management.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Herbal Shampoo: A Review

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A B S T R A C T

Preparing and evaluating a herbal shampoo with an emphasis on the product's safety, effectiveness, and quality is the primary goal of the current study. Herbal shampoo is a natural hair care solution that is used to eliminate grime, dandruff, and grease as well as to encourage hair growth, strength, and blackness. Since shampoos are a common cosmetic item used in daily life, the shampoo industry has the most units sold of any hair care product. Consumers have occasionally experienced negative consequences as a result of synthetic detergents and preservatives. Incorporating natural extracts with similar functionality to their synthetic counterparts is a more extreme method of minimise the use of synthetic compounds. Shampoo is one of the most important beauty items since it helps clean the hair. Herbal shampoo is a cosmetic product similar to ordinary shampoo in that it uses traditional ayurvedic herbs to clean the hair and scalp. They are used to clean up environmental pollutants, dandruff, grease, and grime.

Keywords: Herbal shampoo powder; cleanser; hair care; shampoo; hair detergent; ayurvedic herbal shampoo; hair conditioning; hair cleanser.

1. INTRODUCTION

A shampoo is a mixture of a surfactant (also known as a surface-active substance) in an appropriate form, such as a liquid, solid, or powder, that when used as directed will remove surface grime, filth, and debris from the hair shaft and scalp without having an unfavourable effect on the user (Al badi et al., 2024; Namita, 2013). “In our daily lives, shampoos are likely the most frequently used cosmetic products for cleaning our hair and scalp. A shampoo is essentially a detergent solution with appropriate additives for additional benefits such as improved hair conditioning, lubrication, medication” (Sharma et al., 2011). “There are many different types of shampoos available today, including synthetic, herbal, medicated, and non-medicated varieties, but consumers are becoming more and more interested in herbal shampoo because they think that because these products come from natural sources, they are risk-free and without side effects” (Dubey et al., 2004). “Synthetic surfactants are included in synthetic shampoos mainly for their cleansing and foaming characteristics, but lengthy consumption of these surfactants can produce eye and scalp irritation, hair loss, and hair dryness. We have natural herbal shampoos as an alternative to synthetic shampoo. However, creating cosmetic products with entirely natural ingredients is exceedingly challenging” (Golhani et al.,2015; Godeto et al., 2023).

Fig. 1. Herbal products

"Numerous medicinal plants with possible benefits on hair have been used for centuries in shampoo formulations All worldwide. These therapeutic herbs can be used as extracts, powders, crude forms, or derivatives. It is challenging to create a shampoo with only one natural ingredient that is safer and softer than synthetic shampoo. It must also include considerable foaming, detergency, and solid content, similar to synthetic shampoo. As a result, we gave careful thought to developing a pure natural cleanser employing a time-tested method and commonly used plant material for washing hair" (Balsam et al.,2008).

Anatomy of Hair: Understanding the anatomy of hair is fundamental in comprehending the effects and benefits of herbal shampoos on hair health:

1. Hair Structure: Hair is primarily composed of a protein called keratin, arranged in three layers: the cuticle, cortex, and medulla. The outermost layer, the cuticle, consists of overlapping scales that protect the inner layers and determine the hair's strength and shine. Herbal shampoos often target this layer, aiming to nourish and smoothen the cuticle for enhanced hair texture and appearance (Saraf et al., 2011).

2. Scalp: The scalp is the foundation of healthy hair growth. It contains hair follicles responsible for hair growth and sebaceous glands that produce natural oils (sebum) to moisturise and protect the hair. Herbal shampoos often focus on maintaining a balanced and healthy scalp environment, reducing excess oiliness or dryness while promoting optimal conditions for hair growth (Arora et al., 2019).

3. Hair Growth Cycle: Hair undergoes a growth cycle consisting of three phases: anagen (growth), catagen (transition), and telogen (resting). Herbal shampoos may impact this cycle by nourishing the scalp, potentially prolonging the growth phase and reducing hair fall during the resting phase.

Anagen (growth phase): It is the growing phase. This phase lasts for several years. Catagen (transitional phase): During this phase the hair follicle shrinks and hair growth slows.

Telogen (resting phase): It is the resting phase where hair growth stops and new hair begins the growth phase, pushing the old hair out.

Exogen phase: Last phase of hair growth cycle where hair strand completely detaches from the scalp and sheds off (Sachin Dubey et al., 2004).

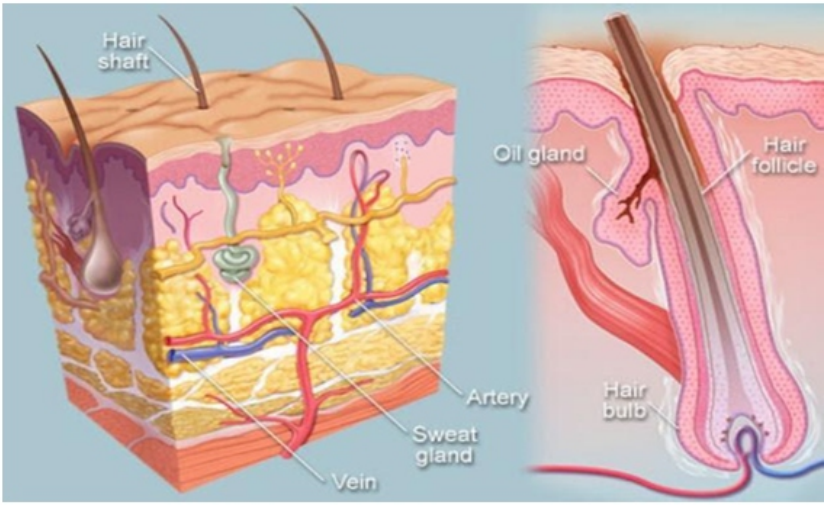

Fig. 2. Hair Structure

4. Hair Porosity: "Porosity refers to the hair's ability to absorb and retain moisture. Herbal shampoos containing moisturising ingredients can aid in regulating hair porosity, preventing excessive loss of moisture and maintaining hair hydration levels. Understanding the intricacies of hair anatomy enables consumers to select herbal shampoos tailored to address specific aspects of hair health, promoting overall nourishment, strength, and vitality" (Shakshi More et al., 2024).

2. PHYSIOLOGY OF HAIR

Hair growth cycle: Hair development a continuous cyclic process and all mature follicles go through a growth cycle consisting of growth (anagen), regression (catagen), rest (telogen) and shedding (exogen) phases. The duration of the phase's changes based on the location of the hair and also personal nutritional and hormonal status and a.

1. Anagen: "The inception of anagen phase is presented by the onset of the mitotic activity in the secondary epithelial germ located between the club hair and dermal papilla in telogen hair follicle. The anagen is the active growth phase in which the follicle enlarges and takes the original shape and the hair

fibre is produced. Almost hair cm^2 on average with variable range of 175-300 hair cm^2. The rate of hair growth has been reported be varying with sites. Scalp and chin have highest rate of growth. The rate of growth of scalp hair is between 0.27-0.40 mm per day. The growth rate of axillary hair is nearly same. The growth rate for hair on surface is about 0.2 mm per day. Though the daily variations of temperature have no effect on the growth rate but the study indicate higher growth rate of beard in summer than winter. Also, there is one study report which indicated that the growth of scalp hair in women is faster than men. The growth rate of scalp hair is more in young and adults and declines in old age" (Gaikwad p.d.et al., 2018).

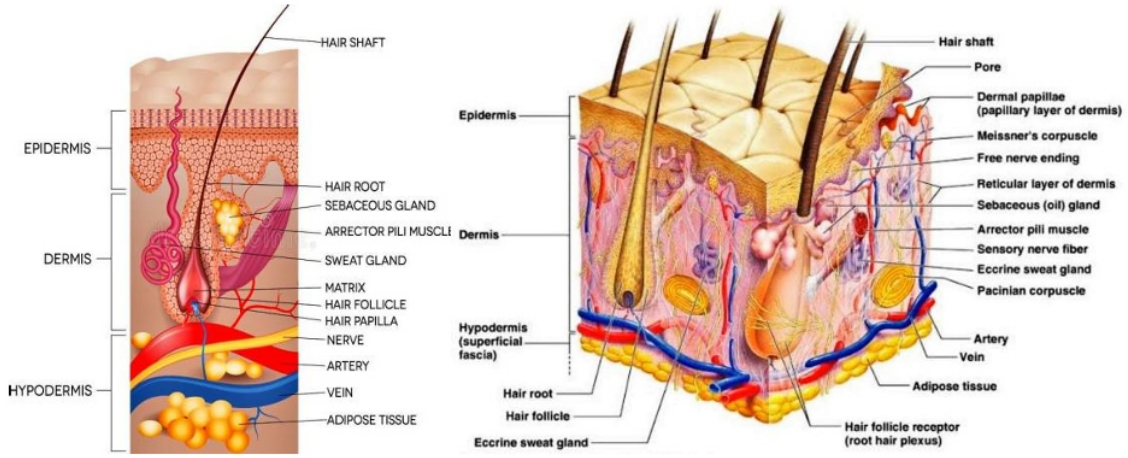

Fig. 3. Physiology of Hair

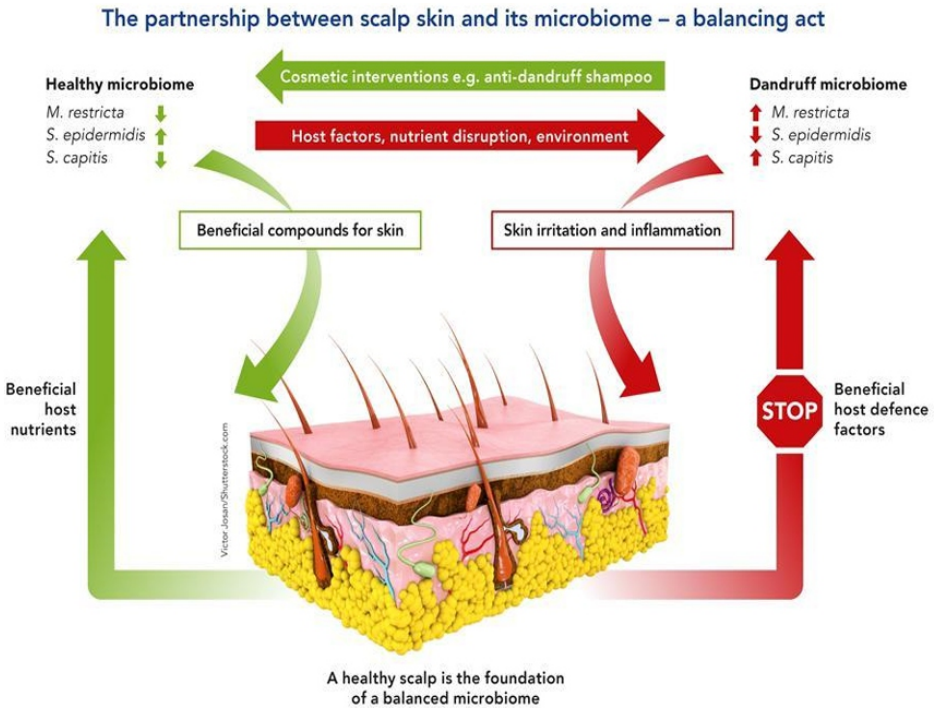

Fig. 4. Parternership between scalp skin and its microbiome

85-90% of all scalp hairs are in anagen. Six portions of the anagen stage are demonstrated. Through the anagens I-V, hair stem cells proliferate, encloses the dermal papilla, grow downwards to the skin and begin to proliferate hair shaft and IRS, respectively.

"Subsequently, hair matrix melanocytes begin to develop pigment and the form of the hair shaft begins to arise: in anagen VI. Hair bulb and adjacent the dermal papilla formation is realized and the new hair shaft appears from the skin. This phase can last up to 6-8 years in hair follicles. Hair shaft synthesis and pigmentation only takes place in anagen. The degree of axial symmetry within thehair bulb determines the curvature of the final hair structure. Fiber length is often dependent on the duration of the anagen or actively growing phase of the follicle" (Gorantla et at., 201e). The featured regulatory proteins in anagen phases are BMP, sonic hedgehog, several WNT proteins and receptors, Insulin like growth factor1 (IGF-1), fibroblast tgrowth factor-7 hepatic growth factor (HGF), and vascular endothelial growth factor (VEGF) are thought to be important for anagen maintenance.

2. Catagen: "At the end of anagen, mitotic activity of the matrix cells is diminished and the follicle enters a highly controlled evolutionary phase known as catagen. Catagen lasts approximately 2 weeks in humans, regardless of the site and follicle type. During catagen the proximal of the hair shaft is keratinized and forms the club hair, whereas the distal part of the follicle is involutedly by apoptosis"

Catagen phase is consisted of eight different stages. The first sign of catagen is the termination of melanogenesis in the hair bulb. Follicular epithelium, mesenchyme,neuroectodermal cells populations and also Perifolliculaar vascular and neural systemsdemonstrates cyclic changes in differentiation and apoptosis. However, any apoptosis is occurred in dermal papilla due to the expression of suppressor bcl-2 (Sapna et al.,2023). "Catagen is a process of bulbar involution. The perifollicular sheath collapses and vitreous membrane thickens. Eventually, the lower hair follicle becomes reduced to an epithelial strand, bringing the dermal papilla into close proximity of the bulge. The epithelial strand begins to elongate and finally reaches to just below the insertion of pilar muscle. After the keratinization of the presumptive club hair, the epithelial strands begin to involute and shorten progressively followed by the papilla which condenses, moves upward and locates to rest below the bulge. The Column eventually reduces to a nipple and forms secondary hair germ below the club. The presence of hairless gene mutation contributes to the failure of dermal papilla migration toward the bulge area in catagen phase" (Pratiksha s sawant et al., 2020).

3. Telogen: "The telogen stage is defined as the duration between the completion of follicular regression and the onset of the next anagen phase. Telogen stage lasts for 2-3 months. Approximately 10-15% of all

hair is in telogen stage. During the telogen stage, the hair shaft is transformed to club hair and finally shed. The follicle remains in this stage until the hair germ which is responsive to anagen initiating signals from the dermal papilla, starts to show enhanced proliferative and transcriptional activity in late telogen, leading to the initiation of anagen. Telogen is one of the main targets of hair cycle which is influenced by several modulator agents like androgens, prolactin, ACTH, retinoids and thyroid hormones. Germ cells of telogen follicles also express bicuculine and FGF-5. The bone morphogenicprotein-4(BMP-4) as a growth factor plays an essential role in suppressing follicular growth and differentiation at telogen stage. The macro-environment surrounding the hair follicle also takes part in regulating cycle transitions. Telogen with a hair germ that is responsive to anagen-initiation signals and capable of entering a new anagen phase" (Preethi et al., 2013).

4. Exogen: "There is less interest for the mechanism of the hair shedding but from the patient's perspective it is probably the most important part of the hair growth. It is not unusual for human telogen hairs to be retained from more than one follicular cycle and this suggest that anagen and exogen phases are independent. The shedding period is believed to be an active process and independent of telogen and anagen thus this distinct shedding phase is named exogen. All body hairs undergo a similar life cycle, although is extent, the duration of its phases and the length of individual shafts vary between different body areas and between individuals, depending on genetic programming, gene, age and health status" (kaveri.j. et al., 2022).

3. HAIR PROBLEM

Hair problems encompass a wide range of conditions that affect the scalp and hair strands, often necessitating specialised care and treatment:

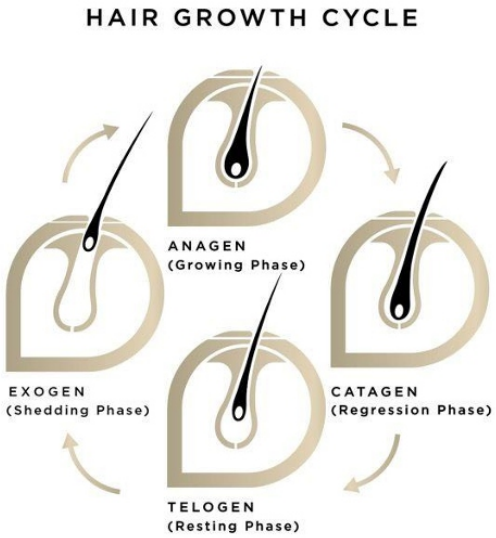

Fig. 5. Hair growth cycle

Fig. 6. Different Hair problems

1.Dandruff: A common issue characterised by flaking of the scalp, caused by various factors such as dry skin, yeast overgrowth, or sensitivity to hair care products. Herbal shampoos with antifungal or soothing ingredients like tea tree oil or aloevera can help alleviate dandruff.

2. Hair Loss: Hair loss or alopecia can result from genetics, hormonal changes, stress, or medical conditions. Herbal shampoos targeting hair loss often contain ingredients like saw palmetto or biotin, aiming to strengthen hair follicles and minimise hair fall.

3. Dryness and Frizz: Dry, frizzy hair occurs due to a lack of moisture and damage to the hair cuticle. Herbal shampoos with hydrating components like coconut oil or shea butter can restore moisture and smoothen the hair shaft.

4. Oily Scalp: Excessive oil production on the scalp leads to greasy, flat-looking hair. Herbal shampoos formulated with clarifying ingredients like citrus extracts or witch hazel can regulate oil production without stripping the scalp of its natural oils.

5. Scalp Irritation: Conditions like scalp psoriasis, eczema, or sensitivity to certain ingredients in hair products can cause itching, redness, or inflammation. Herbal shampoos with gentle, calming ingredients like chamomile or calendula aim to soothe and alleviate scalp irritation. Choosing the right herbal shampoo tailored to address specific hair concerns is crucial in effectively managing and resolving these hair problems, promoting healthier and more resilient hair and scalp conditions.

4. HAIR CARE

"Hair texture and shine are usually related to hair surface properties, on the other hand, the integrity of hair is due to the hair cortex. For this purpose, hair products that improve the structural integrity of hair fibers and increase tensile strength are available, along with products that increase hair volume, reduce frizz, improve hair manageability, and stimulate new hair growth Interestingly, modern cosmetic products are formulated to clean hair from detritus, and to restore and improve hair physiology. For example, intensive conditioning agents can temporarily replace the f-layer, improving the moisture retention in the cortex and rebuilding some of the reduced physical properties of hair. Therefore, the boost in hair shine is a key benefit of modern products" (Bagwan et al., 2022).

5. HOW SHAMPOO WORKS

Shampoo cleans by stripping sebum from the hair. Sebum is an oil secreted by hair follicles that is readily absorbed by the strands of hair, and forms a protective layer. Sebum protects the protein structure of hair from damage, but this protection comes at a cost. It tends to collect dirt, styling products and scalp flakes. Surfactants strip the sebum from the hair shafts and thereby remove the dirt attached to it. While both soaps and shampoos contain surfactants, soap bonds to oils with such affinity that it removes.

Fig. 7. Hair Care

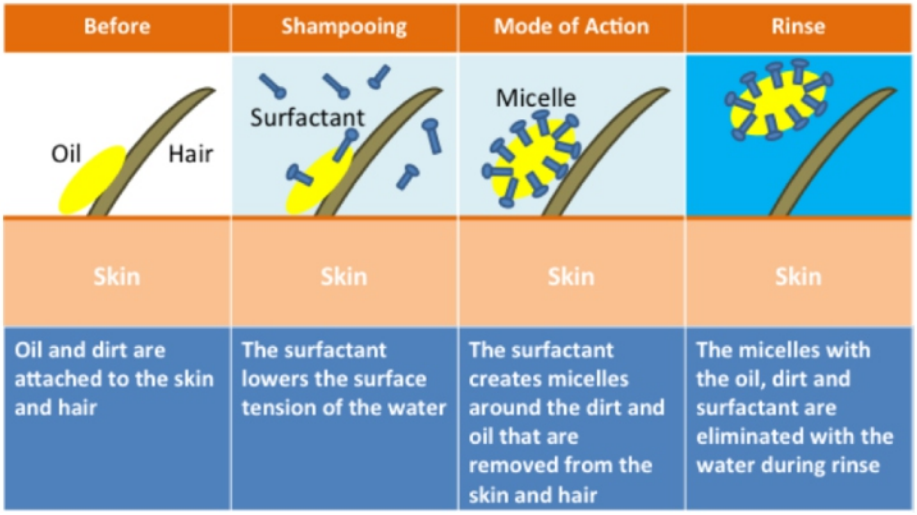

Fig. 8. Mechanism by which herbal shampoo works through a distinct category of surfactants too much if used on hair. Shampoo uses a different class of surfactants balanced to avoid removing too much oil from the hair

The chemical mechanisms that underlie hair cleansing are similar to that of traditional soap. Undamaged hair has a hydrophobic surface to which skin lipids such as sebum stick, but water is initially repelled. The lipids donor comes off easily when the hair is rinsed with plain water. The anionic surfactants substantially reduce the interfacial surface tension and allow for the removal of the sebum from the hair shaft. The non-polar oily materials on the hair shaft are solubilised into the surfactant micelle structures of the shampoo and are removed during rinsing. There is also considerable removal through a surfactant and oil "roll up" off" (Kushwaha R.K.et at., 2022).

6. IDEAL PROPERTIES

• It should fully and efficiently clean the hair of any dust or filth, excessive sebum or other fatty material, and loose corneal cells.

• It ought to be simple to remove with rinse water.

• It shouldn't cause any negative effects like eye or skin discomfort.

• It should provide a pleasant aroma to the hair.

• To give the hair a lustrous, smooth finish.

• Make a significant volume of foam.

• The hand shouldn't get dry and chapped as a result. It ought to successfully and totally eliminate dirt. (Saripalla et al., 2022).

6.1 Benefits of Herbal Shampoo

Natural and Gentle;

1. Sulphate-free: Herbal shampoos are free from harsh sulphates, which can strip the hair of its natural oils.
2. Gentle cleansing: Herbal shampoos clean the hair and scalp without stripping them of their natural moisture.

Promotes Healthy Hair and Scalp:

1. Nourishes the scalp: Herbal shampoos can help to nourish and soothe the scalp, reducing irritation and inflammation.
2. Strengthens hair roots: Herbal shampoos can help to strengthen hair roots, reducing hair fall and promoting healthy hair growth.
3. Improves hair texture: Herbal shampoos can help to improve the texture of the hair, making it soft, smooth, and manageable.

Environmentally Friendly:

1. Biodegradable: Herbal shampoos are biodegradable and free from harsh chemicals that can harm the environment.
2. Cruelty-free: Herbal shampoos are often cruelty-free and vegan-friendly, making them a great choice for those who care about animal welfare.

Customisable:

1. Tailored to hair type: Herbal shampoos can be tailored to specific hair types, such as dry, oily, or combination hair.
2. Address specific hair concerns: Herbal shampoos can be formulated to address specific hair concerns, such as dandruff, itchiness, or hair loss.

Cost-Effective:

1. Long-term benefits: Herbal shampoos may be more expensive than conventional shampoos, but they offer long-term benefits for the hair and scalp.
2. Reduced need for styling products: Herbal shampoos can help to improve the health and appearance of the hair, reducing the need for styling products. (Patel & Talathi, 2016).

Advantages:

• Pure and organic ingredients are used.

• These shampoos are free from side effects.

• No synthetic additives such as sodium lauryl sulphate.

• No animal testing.

• Skin friendly.

• These shampoos help in the strengthening the root which in turn helps in increasing the growth of hair. herbal shampoos also help in increasing the shine of hair therefore for one who suffers from dry and dull hair these herbal shampoos are beneficial.

• It enhances the roots and helps in the formation of new root which are soft then before.

• Herbal shampoos help in reducing the dandruff production in the scalp.

• They may be beneficial in reduction of hair fall

Disadvantages:

• Some herbs are sensitive to scalp. example: menthol.

• Natural products affect product uniformity and quality control.

• Sessional variation of plant constituents occurs.

• Less stable so, preservative should be added.

• Varying in consistency from batch to batch.

• Dry shampoo doesn't clean hair.

• Skin allergies may be occurred (Sharma et al., 2011).

Classification of Shampoo:

1. Based on appearance:

• Powder shampoo

• Liquid shampoo or lotion shampoo

• Gel shampoo or solid shampoo

• Cream shampoo

• Oil shampoo

• Miscellaneous anti dandruff shampoo or medicated shampoo

2. Based on use or function:

• Conditioning shampoo

• Antidandruff shampoo
• Therapeutic shampoo
• Baby shampoo
• Balancing shampoo
• Clarifying shampoo

3. Based on origin:

• Herbal shampoo
• Egg shampoo

Evaluation of shampoos

comprises the quality control tests including visual assessment and physiochemical controls such as ph, density and viscosity (Nagajyothi et at., 2014).

Table 1. Description of Herbal Shampoo ingredients

Common Name	Botanical name	Parts used	Purpose	Category	Picture
Drumstick	Moringa Oliefera	Seed	Anti-dandruff, Anti-microbial	Core ingredient	
Aloevera	Aloe Barbadensis	Pulp	Hair conditioner, control greasy hair	Smoothing agent	
Hibiscus	Rosa Sinesis	Flowers	Improve overall health of hair and scalp	Conditioning agent	
Shikakai	Acacia concinna	Fruits	Scalp health, lousy hair, hair conditioning	Antifungal, Nourish follicles, Curb dandruff	
Ritha	Sapindusmukorossi	Fruits	Reduces frizz and adds shine,soften hairs	soapberry, soapnut, washnut, aritha.	

Sodium Lauryl Sulphate	Sodium dodecylsulfate	Powder	Cleanser, creates lather	Fat Emulsifier, Wetting agent, Detergent in Cosmetics.	
Methyl Cellulose	Hypromellose	Powder	Thickener and emulsifier	Thickening Agent, Stabilizing Agent.	
Rose Water	Rosa damascena	Liquid	Hydration, improves low porosity hair	Flavoured water, Perfume agent	

Formulation of Herbal Shampoo:

Method of Preparation:

1. Weighed all the ingredients according to the formulas.
2. Decoction of Drumstick, Aloevera, Hibiscus was prepared in one part of water.
3. Filter it by using muslin cloth, collect filtrate
4. Decoction of shikakai and Ritha was prepared in another part of water.
5. Filter it, by using muslin cloth, collect filtrate.
6. Mixed to each other of above filtrate with constant stirring.
7. Mixed to sodium lauryl sulphate in foaming.
8. Mixed to methyl cellulose as a thickening agent tom maintenance of consistency herbal shampoo of as per like semisolid mixtures.
9. Preservatives arts and & Rose water this perfume was add Lastly.

Table 2. Ingredients of Herbal Shampoo

S. No	Ingredients	Quantity
1.	Drumstick	10 gm
2.	Alovera	5 ml
3.	Hibiscus	4 ml
4.	Shikakai	8 gm
5.	Ritha	8 gm
6.	Sodium Lauryl Sulphate	6 gm
7.	Methyl Cellulose	1 gm
8.	Rose Water	10 ml

Evaluation of Herbal Shampoo:

Appearance: A shampoo like any other cosmetic preparation should have good.

Appealing physical appearance: The formulated and marketed shampoos were evaluated for physical characteristics such as colour, odour and transparency (Table 3). Our prepared shampoo was transparent, light green and had good odour. No significant difference was observed in terms of odour, transparency and foaming characteristics between commercial and formulated shampoo except for colour.

Colour: Black Brown, Dandruff Cleansing Shampoo

PH: The pH of formulated shampoo was 6, falling within the ideal pH range for shampoo which is between 4.33 and 4.73. The formulated shampoo is acid balanced which is near to the skin PH. The pH of shampoo is important for improving and enhancing the qualities of hair, minimising irritation to the eyes and stabilising the ecological balance of the scalp. Mild acidity prevents swelling and promotes tightening of the scales, there by inducing shine.

Viscosity: The viscosity of shampoo plays an important role in determining its shelf life stability, the ease of flow on removal from packing and spreading on application to hair and product consistency in the package. The viscosity of formulated shampoo was found to be 50 millipoise which was good enough for its applicability.

Foaming Stability: The stability of the foam was determined using cylinder shake.

Method. About 50 ml of formulated shampoo (1%) solution was taken in a graduated cylinder of 250 ml capacity and shaken for 10 times vigorously. Foam stability was measured by recording the foam volume of shake test after 1 min and 4 min, respectively. The total foam volume was measured after 1 min of shaking. From the consumer point of view, foam stability is one of the important needs of a shampoo. Important parameter that was considered in the shampoo evaluation was determination of foaming stability. The foam volume produced by the formulated shampoo is above 50 ml. The prepared shampoo generates uniform, small sized, compact, denser, and stable foam. The foam volume remains same throughout the period of about 5 min showing that the generated foam by the shampoo has good stability.

Surface Tension: Measurements were carried out with a 10% shampoo dilution in distilled water at room temperature. Thoroughly clean the stalagmometer using chronic acid and punitied water. Because surface tension is highly affected with grease or other lubricants.

Wetting time: Wetting time was calculated by noting the time required by the canvas paper to sink completely. A canvas paper weighing 0.44 g was cut into a disc of diameter measuring 1-inch. Over the shampoo (1% v/v) surface, the canvas paper disc was kept and the time taken for the paper to sink was measured using the stopwatch.

Cleaning action: About 1 g of grease is spread on non-adsorbent cotton and kept in conical flask containing 1% shampoo solution. The conical flask is shaken for 1 hr in mechanical shaker. Cotton is collected, dried and weighed.

Dirt dispersion: Shampoo that causes the ink to concentrate in the foam is considered poor quality; the dirt should stay in water. Dirt that stays in the foam will be difficult to rinse away. It will redeposit on the hair. The estimated amount of ink in foam was light and so results indicate that prepared formulation is satisfactory.

Solid contents (%): A Clean dry china dish was weighed and 4 grams of shampoo was added to it. The weight of dish and shampoo was noted. The exact weight of shampoo was calculated. Place the china dish with herbal shampoo on hot plate until the liquid portion was evaporated. The weight of shampoo (solids) after drying was calculated (Pawan Maurya et al.,2021).

7. POWDER SHAMPOO

7.1 Description of Powder Shampoo Ingredients

Table 3. Description of powder shampoo ingredients (Pal R.S.et al.,2020)

Common Name	Botanical Name	Parts Used	Category	Purpose	Picture
Shikakai	*Acacia concinna*	Fruit pods,leaves	Natural foaming agent	Foam base and Anti-dandruff	
Reetha	*Sapindus mukorossi*	Dessicated fruit	Natural surfactant and cleanser	Hair nourishing and cleansing	

Tulasi	*Ocimum tenuiflorum*	Dried leaves	Anti fading	Antibacterial	
Amla	*Phyllanthus emblica*	Dried ripe fruits	Hair growth promoter	Hair health, scalp health	
Neem	*Azadirachta indica*	Neem leaves and extracts	Anti-dandruff	Improve greying of hair	
Henna	*Lawsonia inermis*	Dried leaves	Hair colourant	Conditioner	
Harda	*Terminalia chebula*	Dried ripe fruits	Anti-inflammatory, Anti-bacterial	Hair growth promoter	
Bhringraj	*Eclipta prostrata*	Entire herb	Hair growth promoter	Promote the hair health	

Table 4. Formula of herbal dry shampoo powder (pawar A.et al.,2022).

Ingredients	Quantity 100gm
Shikakai	15 gm
Reetha	10 gm
Tulasi	10 gm
Amla	15 gm
Neem	5 gm
Harda	10 gm
Henna	15 gm
Bhringraj	5 gm
Black tea	5 gm
Hibiscus flower	10 gm

7.2 Preparation of Dry Shampoo Powder

1. Drying

All the powder are in dry form and grinded.

2. Size reduction

The crude ingredients were collected and these ingredients were size reduced using driven mixer individually.

3. Sieving

Then this fine powder was passed through sieve no.:80, to get the sufficient quantity of fine powder.

4. Weighing

All the required herbal powders for shampoo preparation were individually.

5. Mixing

All these fine ingredients were mixed throughly by mixer to form a homogeneous fine powder.

6. Packing and Labeling

Then it was packed and labeled suitably. (Pundhkar A. et al. (2020).

7.3 Evaluation of Herbal Shampoo

Organoleptic evaluation: Organoleptic evaluation on the parameters like colour, odour taste and texture was carried out. Colour and texture was evaluated by vision and touch sensation respectively. For taste and odour evaluation a team of five taste and odour sensitive persons was formed and random sampling was performed.

General powder characteristics: General powder characteristics includes evaluation of those parameters which are going to affect the external properties (like flow properties, appearance, packaging criteria etc.) of the preparation, Characteristics evaluated under this section are powder form, particle size angle of repose and bulk density. Sample for all these evaluation were taken at three different level i.e. from top, middle and lower level. Particle size.

Particle size is a parameter, which affect various properties like spreadability, grittiness etc., particle size was determined by sieving method by using I.P. Standard sieves by mechanical shaking for 10 min.

Angle of repose: It is defined as the maximum angle possible in between the surface of pile of powder to the horizontal flow.

Funnel method: Required quality of dried powder is taken in a funnel placed at a height of 6 cm from a horizontal base. The powder was allowed to flow to form a heap over the paper on the horizontal plane. The height and radius of the powder was noted and recorded the angle of repose (θ) can be calculated by using the formula.

Open - ended cylinder method: Required amount of dried powder is placed in a cylindrical tube open at both ends is placed on a horizontal surface.

Then the funnel should be raised to form a heap. The height and radius of the heap is noted and recorded. For the above two methods, the angle of repose (θ) can be calculated by using the formula.

$$\theta = \tan^{-1}(h / r)$$

Where,

θ – Angle of repose, h – Height of the heap, r – Radius of the base

Bulk density: Bulk Density is the ratio between the given mass of a powder and its bulk volume. Required amount of the powder is dried and filled in a 50 ml measuring cylinder up to 50 ml mark. Then the cylinder is droppedonto a hard wood surface from a height of 1 inch at 2 second intervals. The volume of the powder is measured. Then the powder is weighed. This is repeated to get average values. The Bulk Density is calculated by using the below given formula.

Mass of the herbal powder shampoo:

$$Bulk\ Density = \frac{Mass\ of\ the\ herbal\ powder\ shampoo}{Volume\ of\ the\ herbal\ powder\ shampoo}$$

Tapped density: The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped for 1 min and volume or mass readings are taken until little further volume or mass change was observed. It was expressed in grams per cubic centimeter (g/cm3) (Namita, 2013).

8. POLY HERBAL ANTI DANDRUFF SHAMPOO

Table 5. Description of Poly herbal anti dandruff shampoo ingredients (Singh et al.,2021)

Common name	Botanical name	Part used	Category	Purpose	Picture
Neem	*Azadirachta indica A. Juss*	Fresh Leaves	Antifungal/ Antibacterial	Improve greying of hair	
Bhringraj	*Eclipta alba (L.) Hassk*	Powder of Leaves	Antifungal/ Antibacterial agent	Promote the hair health	
Shikakai	*Acacia concinna Linn*	Leaves	Natural foaming agent	Scalp health, lousy hair, hair conditioning	
Fenugreek	*Trigonella foenum-graecum L.*	Seeds	Anti dandruff	Reduce the premature greying of hair	
Reetha	*Sapindus trifoliatus linn*	Seeds	Natural surfactant and cleanser	Hair nourishing and cleansing	
Aloe Vera	*Aloe barbadensis miller*	Latex of Leaves	Smoothing agent	Hair conditioner, control greasy hair	

Common name	Botanical name	Part used	Category	Purpose	Picture
Lemon Juice	*Citrus limon (L.) Burm*	Fresh Ripe Fruit Juice	Anti dandruff	Enhance hair shine, remove excess oil	
Tulsi	*Ocimum sanctum L*	Fresh Leaves	Anti fading, Anti scalp inflammation	Antibacterial	
Orange	*Citrus Linn.*	Pericarp	Antibacterial	Reduce lousy hairs	
Ginger	*Zingiber officinale Roscoe*	Rhizome	Hair promoter	Improve blood circulation	
Curry Leaves	*Murraya koenigii Linn.*	Fresh Leaves	Hair strengthen	Shine & strong the hairs	
Hibiscus	*Hibiscus-sinensis L*	Fresh Leaves.	Conditioning agent	Improve overall health of hair and scalp	

Table 6. Formulation of poly herbal anti dandruff shampoo

Ingredients	Quantity(100ml)
Herbal extract	24ml
Sodium Lauryl Sulphate	6gm
Guar gum	1gm
NaCl (0.1M)	Q. s
Glycerin	2ml
Vitamin E	800mg
Lavender oil	2 drops
Water	Q. s100ml

9. PREPARATION OF POLY HERBAL ANTI DANDRUFF SHAMPOO

• The composition was made by simple decoction process.
• All the herbs were accurately weighed by using digital balance the used quantity is listed in Table 1.
• The crude herbs were collected and these ingredients were size reduced using hand driven mixer individually grinded into powder, fine powder was passed through sieve no.120 and separately mixed with 100ml distilled water and kept for boiling till water gets reduced to one quarter.
• After boiling, the extract was cooled at normal room temperature and then filtered with muslin cloth to get the final filtrate (Sravanthi et al.,2021).

10. EVALUATION PARAMETERS FOR ANTI DANDRUFF SHAMPOO

1. PH: 10% v/v shampoo solution is prepared in distilled water and pH of this solution was measured with digital pH meter at room temperature 30-2°C

2. Determination of percentage solids content: A clean dry dish was weighed and added with 4 Grams of shampoo. The dish with shampoo was weighed. The exact weight of the shampoo was calculated. The dish with shampoo was placed on the hot plate until the liquid portion was evaporated. The weight after drying was calculated (10).
3. Wetting time (sec): A cotton ball weighing of about 0.44gm was taken and added it to container containing shampoo Time taken for cotton to sink at bottom of the formulation was measured as wetting tune
4. Viscosity: The index of resistance to flow was determined using Brookfield viscometer DV-II Pro at room temperature Lc. 30+2°C with varying rpm and torque
5. Surface tension measurement: Dilute the shampoo using distilled water to fix 10% as concentration. Measurements were carried out using stalagnometer
6. Foam formation/Foam stability: Cylinder shake method Used. 50ml of 1% solution of shampoo is taken in graduated cylinder (1 ml in 100ml water), shake for ten minutes and record the foam produced after I minute. Record the stability of foam after 4-5 minutes+_2 for 48 hand examined for the appearance of inhibition zones around the wells. The diameters of the inhibition zones were measured from the images using digital antibiotic zone reader.
7. Stability studies: Stability studies were performed in accordance with KH guidelines for accelerated testing with required modifications. The sample taken formulation was taken and kept at room temperature (30 2°C) a well as refrigerator (4:2°C) for duration of one month The samples were tested for their physical appearance, PH, viscosity, cleaning action and foam stability.

8. In vitro anti-dandruff activity: Well diffusion assay method was used. The anti-microbial efficiency of polyherbal anti dandruff Shampoo was examined against Malassezia furfur using an agar well diffusion assay method. 500µl fungal cell suspension was spread onto the Sabourand Dextrose Agar (SDA) plates and wells (mm diameter was made on the agar plates using a sterilized stainless steel cork borer). The wells were landed with 20µl of the respective shampoo. The plates were incubated at 35 °C.

9. Address specific hair concerns: Herbal shampoos can be formulated to address specific hair concerns, such as dandruff, itchiness, or hair loss (Saraf et al., 2011).

11. CONCLUSION

The key to choosing the best shampoo is knowing your particular hair needs, which include your hair type, scalp health, and desired results. While washing is the primary function, modern shampoos usually provide additional benefits like hydration, volume, or color retention. For the best possible hair health and appearance, it is essential to select a shampoo that targets your unique hair issues for which the herbal shampoo is chosen which is suitable for almost all hair types and it leaves no side effects and less added artificial agents.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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