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Formulation And Evaluation of Herbal Suppositories Containing Guggul for The Treatment of Piles

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Abstract
The aim of this research was to formulate and evaluate herbal suppositories containing guggul as a chief herbal drug for the treatment of piles. The suppositories were formulated using extracts of guggul, tridax procumbanas, and haritaki. guggul and haritaki are used as anti-inflammatory agents, and tridax procumbans is used as an antiseptic agent. Polyethylene glycol 4000 and beeswax are used as a suppository base. The formulated suppositories were evaluated for parameters including visual appearance (fissuring, pitting, fat blooming, exudation of active ingredient), length and width, weight variation, melting point, disintegration test, and in vitro anti-inflammatory activity by using the protein denaturation method and the protein inhibition method. The physical parameter was found to be within acceptable limit. The anti-inflammatory activity revealed the formulated suppositories has comparable anti-inflammatory activity as compared to standard drug diclofenac sodium (56.64 % vs 64.16%).

Introduction

Hemorrhoids, often known as piles, are enlarged veins in the lower rectum and anus that resemble varicose veins [1]. These are very prevalent anorectal disorders that are characterized by symptomatic swelling and distal displacement of the normal anal cushions. Hemorrhoids have been associated with humans as a disease entity since the dawn of recorded history. Half of men and women of any age suffer hemorrhoid symptoms at some point in their lives, making hemorrhoids a prevalent condition among adults. However, women between the ages of 45 and 65 are more likely to experience it than men [2].

Internal hemorrhoids were the third most frequent colonoscopic finding, or 7.5%, according to a study conducted at Ayder Referral Hospital. 13.1% of adult patients who went to the surgical outpatient department at the University of Gondar comprehensive specialty hospital, according to a different survey, had hemorrhoids. Hemorrhoids are typically categorized according to where they are and how much prolapse they have. Turelly claimed that 40% of the population requires surgical treatment for hemorrhoids, which afflict 70% of the population. Internal hemorrhoids form within the rectum, while external hemorrhoids form beneath the skin around the anus. It is often diagnosed as a hemorrhoidal plexus inflammatory condition [3].

One of the most widespread illnesses to affect people, internal hemorrhoids are characterized by bleeding and prolapse. Internal hemorrhoids might prolapse during urination and bleed painlessly in brilliant crimson [4].

External hemorrhoids are anoderm-covered and located distal to the pectinate line; while they may grow, making personal hygiene challenging, they only truly cause serious pain when they become Major symptoms associated with hemorrhoid complaints include inflammation, pain, bleeding and pruritus. Treatment available for hemorrhoids mainly include laser treatment, sclerother-apy, hemorrhoidectomy, infrared photocoagulation and bipolardiathermy [5].

However, oral route become unsuitable in some cases such as nausea, vomiting or convulsion. In such cases, the rectal route may offer a suitable alternate. Rectal route is also preferred if the drug is extensively metabolized or deactivated by liver enzymes [6].

When a medication is heavily metabolized or rendered inactive by liver enzymes, the rectal route is also flavoured. According to reports, the absorbed medications are discharged into the portal vein, then the liver, via the superior hemorrhoidal veins. The lower region of the rectum is drained by the middle and inferior hemorrhoidal veins, and venous blood is then redirected to the inferior vena cava. The medicine will therefore start to circulate throughout the body, avoiding the liver, once it is absorbed in the latter system. The best treatment for hemorrhoids is rectal suppositories. Suppositories are typically placed after a bowel movement, which prolongs the duration of the medication's effects because they degrade more gradually. Rectal tissue absorbs the medication, which can be beneficial [7-8].

Currently, herbal medicines are becoming the major alternatives for management of different diseases.

Nearly 90% of Ethiopians depend on traditional medicine, mainly herbal medicine, for managing their illnesses . Hemorrhoids was reported as the fourth most commonly treated disease by traditional healers in Addis Ababa, Ethiopia" bortifacient activities [9].

Scientifically, the plant is reported to have an anti-inflammatory and antiseptic activity while, traditionally the leaves of the plant are used in treatment of hemorrhoids, which is still unexplored. Thus, taking these evidences into consideration, the present investigation was undertaken to scientifically validate the anti-hemorrhoidal potential of leaves from the plant commiphora weightii, terminalia chebula, tridax procumbans. These plants have anti-inflammatory and antiseptic activity which has been useful for piles Currently, herbal medicines are becoming the major alternatives for management of different diseases. Nearly traditional healers in Addis Ababa, Ethiopia" bortifacient activities.

Cammiphora weightii, or guggul. (Arnott) Commiphora wightii A flowering plant in the Burseraceae family is called bhandari. The gum resin (guggul) or fake myrrh of Commiphora wightii has been widely utilized in Indian traditional medicine to treat patients with a variety of illnesses, including rheumatoid arthritis, inflammation, obesity, and hyperlipidaemia. Guggul has a wide range of pharmacological qualities, including anti-microbial, anti-inflammatory, and anti-cancer effects, as shown by other studies [10].

Haritaki / terminalia chebula The medium- to large-sized Terminalia chebula Retzius (T. chebula Retz) tree is found all throughout Asia and is a member of the Combretaceae family. Human health issues like digestive, tonic, antipyretic, spasmolytic, astringent, expectorant, anti-asthmatic, antiviral, and antiviral hypoglycemia disorders are frequently treated using ayurvedic treatments. The leaves, fruits, seeds, and bark of this evergreen, blooming tree are frequently utilized in traditional folk medicine. Anti-bacterial, antifungal, anti-carcinogenic, antioxidant, antidiabetic, anti-inflammatory, antiHIV, and anti-aging properties are all present in this plant. Bioactive substances such as tannins, flavonoids, sterols, amino acids, fructose, and resins are abundant in T. chebula [11].

Tridax procumbans The flowering plant Tridax procumbens is a member of the Asteraceae family. It comes from the US but is now sold all over the world and is commonly referred to as cotton buttons. It has historically been used to treat metabolic problems, infections, malaria, and wound healing. Tridax procumbens has been scientifically proven to have a number of beneficial properties, including antibacterial, anti-hyperuricemic, antioxidant, and antipurgative effects, as well as the ability to treat wounds and acute diseases. The crude extract of T. procumbens has been shown in prior research to inhibit amylase, lower blood sugar levels, and improve lipid levels in diabetic rats [12].

Material and method

Material

Powder of guggul (*commiphora weghtii*) and haritaki (*terminalia chebula Retz)* were purchase from local market. The leaves of plant tridax procumbans were collected from herbal garden of SVERI's College of Pharmacy Pandharpur and authentification of these drug will be done at KBP Mahavidyalay,Pandharpur. Diclofenac sodium was obtained from Jb Pharma, Thane.

Phytochemical Evaluation

1. Carbohydrate test

Fehling's test: Fehling A and Fehling B reagents were mixed together in equal volume, and 2 ml excerpt was added, boiled in a water bath, and cooled. The appearance of slipup-red precipitate at the bottom of the test tube.

2. **Flavonoid test:** NaOH and HCL test 2 ml of excerpt was treated with waterless NaOH and HCL and observed for the conformation of a unheroic-orange color.

3. **Alkaloid test:** A many drops of Mayer's reagent were added to 1 mL of excerpt. A yellowish or white precipitate was formed, indicating the presence of alkaloids.

4. **Glycoside**
   Killer- Kilani: The 2 ml of extract was taken in the test tubes, and 1 ml of glacial acetic acid and ferric chloride was added. To this 1 ml of concentrated sulfuric acid was added to the admixture. A brown- multicolored ring at the edge will be formed, which shows the presence of glycosides.

5. **Saponin test**: 2 ml of extract was dissolved into 5 ml of distilled water. was shaken for proper mixing until froth was produced.

6. **Tanin test**: The 2 ml of extract was mixed with 0.5 ml of ferric chloride result. The presence of tannin causes the conformation of palish precipitate.

7. **Steroid test**: 2 ml of extract was mixed with 1 ml of chloroform, and to this concentrated sulfuric acid and acetic acid were added. The greenish color indicated the presence of steroids.

8. **Amino acid:** 2 ml of extract was mixed with 1 ml of amino acid and the mixture was was taken in a test tube and ninhydrin reagent was added. Place the test tube on water bath for 5 min. Also cool to room temperature (14-16).

Method of isolation:

Tridax procumbans leaves were collected from the botanical garden and the leaves were washed with water, and the rind was removed. The leaves were solar dried for two weeks and the powder was screened through a sieve No.16 and used for further studies.

Method of extraction
Maceration method
The 100-gm powder of Tridax procumbans was dissolved in 400 ml of ethanol, and the 100-gm powder of Guggul was dissolved in 200 ml of ethanol. The mixture was kept aside until the powder dissolved completely and then kept for distillation to separate the ethanol, and the final extract was collected in china dish and used for further studies [17-19].

Formulation of suppositories:

Haritaki / Decoction method:
Haritaki powder was extracted by the decoction method using water as a solvent. 100 g of powder were dissolved in 400 ml of water. The dissolved mixture was heated for 1 hour on the heating mentle, and the final extract was collected in china dish and used for further studies **[**20].

Preparation of suppositories:
The bases polyethylene glycol 4000, methyl paraben, and beeswax, were accurately weighed and melted in a china dish. The divided extract was thoroughly incorporated into the melting base with continuous stirring. The melted mass was poured into the appropriate suppository mold. The suppositories were kept in the refrigerator at 4 °C To avoid the development of cracks [21].

TABLE NO.1: FORMULATION OF SUPPOSITORY

Ingradients	**F1**	**F2**	**F3**
Guggul	600mg	550mg	500mg
Tridax procumbans	25mg	20mg	15mg
Haritaki	125mg	100mg	75mg
PEG4000	0.200ml	0.150ml	0.100ml
Bees wax	1.200mg	1.150mg	1 mg
Methyl paraben	350mg	230mg	200mg

Physical parameter of suppositories:
1. Visual characterization: Six suppositories were from each group. Colour, odour, shape, the absence of fissuring, pitting, sedimentation were assessed.

2. Length and width: Suppositories were named from each batch, and their length and width were measured by a vernier calliper.
3. Weight variation: The weight uniformity test was carried out as designated in the British Pharmacopoeia (BP, 2013). Ten suppositories were chosen from each batch and counted singly using an analytical balance. The average weights were calculated.

4. Melting point: The melting point of suppositories were determined according to the fashion of Adebayo and Akala (2005). A suppository named from each batch was put in a china dish with a thermometer introduced. The china dish was immersed in a water bath and controlled to a steady temperature rise of 37 °C. The temperature at which the suppository sample began to melt was taken as the melting point. The melt time plays a crucible role in the release of active constituents.

5. Disintegration test: The disintegration test of suppositories was performed using the disintegration test apparatus. Phosphate buffer Ph 7.2 is maintained at 37 °C. The time taken for the disintegration of entire suppositories was recorded.

6. Hardness test: The hardness tests of suppositories were performed using Monsanto tablet hardness tests [22-23].

7. In-vitro anti-inflammatory activity by Protein denaturation method:
Invitro Anti-inflammatory activity of the formulation was evaluated by protein denaturation method. Diclofenac sodium, a powerful NSAID was used as a standard drug. The reaction mixture consisting of 2 mL of different concentrations of selected herbal drugs mixture or standard diclofenac sodium and 2.8 mL of phosphate buffered saline (pH 6.4) and incubated at 27°C for 15 min. Denaturation was induced by keeping the reaction mixture at 70°C in a water bath for 10 min. After cooling, the absorbance was measured at 660 nm against double distilled water.

$$\% \text{ inhibition} = \frac{Ac-At}{Ac} \times 100$$

Where, At =absorbance of test sample; and Ac=absorbance of control

In -Vitro anti-inflammatory activity by proteinase inhibitory method:
The 1% bovine serum albumin solution was prepared and added to each test samples containing varying concentrations of herbal drugs mixture. The trypsin, 250 µl was added after keeping the mixture at a room temperature for 5 min. Later the mixture was centrifuged and absorbance of supernatant at 210 nm was calculated using a UV- Visible spectrophotometer.

All the samples were evaluated in triplicates. (n=3) [22].
Percentage inhibition of proteinase activity was calculated by using the following formula:

$$\% \text{ inhibition} = \frac{Ac - At}{Ac} \times 100$$

Where, At =absorbance of test sample; Ac=absorbance of control [24].

Result and discussion:
The selected herbal drugs guggul, haritaki, and tridax procumbans are known for their anti-inflammatory activity in suppositories, and traditionally they are used in the treatment of hemorrhoids. Thus, taking this evidence into consideration, the present investigation was undertaken to scientifically validate the anti-hemorrhoidal potential of these herbs (commiphora weightii, terminalia chebula,and tridax procumbans) and herbal suppositories were prepared.
There were no fissures, pits, or cracks in any of the suppositories. The suppositories' longitudinal section is plain and simple. Table 5 displays the conclusions from various evaluation criteria. All of the suppositories' weight fluctuation studies revealed that they were all within the allowed range of 5%, proving that the mold's calibration was accurate. To facilitate handling and shipment, the suppositories should be mechanically strong. All of the suppositories had good mechanical strength between 1.50 and 4.00 kg/cm2, indicating ideal hardness. It is important to consider a pharmaceutical preparation's pH since it shows whether the preparation is compatible with the site of action. Suppositories had a pH that was comparable to the rectum's, which ranges from 6 to 8. If the pH of the suppositories is somewhat acidic (5.12–5.20), this can irritate the rectal mucosa. Stability at room temperature, or the capacity to dissolve or melt at body temperature in order to release the active ingredient, is one of the most crucial qualities of suppository bases. Typically, the melting point should be lower than or equal to 37 °C. It is clear that adding guggul lowered the suppositories' melting point.

Preformulation studies of Crude drugs:
Morphological features of crude drug
The present study shows the morphological features i.e (colour,odour and taste) of given crude drug.

TABLE NO.2: MORPHOLOGICAL FEATURES OF CRUDE DRUG

Morphological features of drug	Guggul	Haritaki	Tridax procumbans
Colour	Dark brown	Brown	Green
Odour	Balsamic	Strong pungent	Characterstic
Taste	Bitter aromatic	Bitter	Slight bitter

Solubility of drug:
Present investigation showed that the solubility of herbal drug in water,ethanol,and ether.

TABLE NO.3:SOLUBILITY OF DRUG

Solvent	Guggul	Haritaki	Tridax procumbans
Water	Soluble	Soluble	Sparingly soluble
Ethnol	Soluble	Sparingly soluble	Soluble
Ether	Slightly soluble	Sparingly soluble	Soluble

Phytochemical evaluation:
[presence of chemical constituent (+) absence of chemical constituent (-)]
The selected herbal drug has shown the presence of all chief chemical constituent as per earlier studies. Thus, it has been certified the authenticity of herbal drug [14-16].

TABLE NO.4: PHYTOCHEMICAL EVALUATION

Sr. No.	Chemical Constituents	Guggul	Tridax Procumans	Haritaki
1	Carbohydrate	+	+	-
2	Flavonoid	-	+	+
3	Alkaloid	-	+	+
4	Glycoside	-	+	+
5	Saponin	-	+	+
6	Tannin	-	+	+
7	Amino acid	+	+	+
8	Steroid	+	+	+

Physical parameter of suppositories:
The prepared suppositories were green in color with a smooth, shiny surface. Furthermore, they were well formed and homogenous in shape. They did not show any fissures, cracks or concentration holes. The weight variation was carried out and it was found that all the prepared suppositories were within the pharmacopoeial limits for the uniformity of weight as

shown in Table 5. The hardness of the prepared suppositories ranged from 3.50 to 5.0 kg. These results showed the good mechanical properties for the suppositories and a higher resistance to fracture during the handling, packaging, transport and insertion. the capacity to dissolve or melt at body temperature in order to release the active ingredient, is one of the most crucial qualities of suppository bases. Typically, the melting point should be lower than or equal to 37 °C. It is clear that adding guggul lowered the suppositories' melting point. The disintegration test apparatus is used to calculate the time taken by the suppositories to fully disintegrate in the medium. Phosphate buffer pH 7.2 maintained at 37±0.5°C was used for the disintegration.

TABLE NO.5: PHYSICAL PARAMETER

Formulation	Length (cm)	Width (cm)	Weight variation(g)	Hardness (kg/cm)	Disintegration Time time(min)	Melting Point 37 (min)
F1	2.1	0.9	1.86	2.1	8	41
F2	1.9	0.8	1.55	2	6.8	40
F3	1.8	0.8	1.46	1.9	6	38

Invitro Anti-inflammatory test by protein denaturation assay of herbal suppositories.
Denaturation of tissue protein is one of the well-reported causes of inflammation. Prevention of protein denaturation can effectively reduce inflammation in such cases In order to determine the Anti-inflammatory activity of the formulation, a protein denaturation assay was performed. Protein denaturation was found to be 56.64% compared to the marketed formulation of Diclofenac sodium (64.16%). This result showed that suppositories might be effective to inhibit protein denaturation in anti-inflammatory process.

TABLE NO.6: IN-VITRO ANTI-INFLAMMATORY ACTIVITY BY PROTEIN DENATURATION ASSAY OF HERBAL SUPPOSITORIES

Sample	Concentration (µg/ml)	Invitro anti-inflammatory activity	
		Absorbance at 660nm	%inhibition
Blank		1.2	
Diclofenac sodium	500	0.54	55.20%
	1000	0.43	64.16%
Suppositories formulation	500	0.62	48.33
	1000	0.51	56.64%

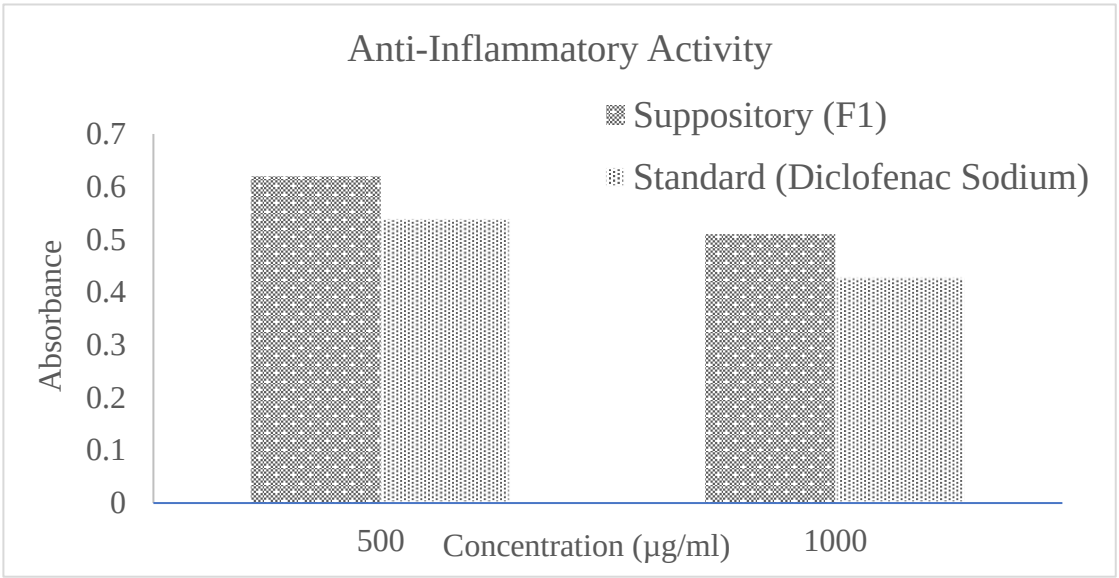

FIG.NO.1: ANTIINFLAMMATORY ACTIVITY BY PROTEIN DENATURATION ASSAY

Proteinase inhibitory method and protein denaturation assay of herbal powder:
Assay were carried out to determine anti-inflammatory activity of guggul powder. The % Proteinase inhibition was found to be 39.20 % as compared to marketed formulation Diclofenac sodium was found to be 48.20%. Protein

denaturation was found to be 41.20 % compared to marketed formulation Diclofenac sodium 51.30 %.
Assay were carried out to determine anti-inflammatory activity of haritaki powder. The % Proteinase inhibition was found to be 36.50 % as compared to marketed formulation Diclofenac sodium was found to be 47.60%. Protein denaturation was found to be 38.80% compared to marketed formulation Diclofenac sodium 50.40%.

TABLE NO.7: PROTEIN INHIBITORY METHOD AND PROTEIN DENATURATION METHOD

Sr No	Batch	Guggul		Haritaki	
		Protein inhibitory method (%)	Protein denaturation assay (%)	Protein inhibitory method (%)	Protein denaturation assay (%)
1	Standard	48.20	51.30	47.60	50.40
2	F1	39.20	41.40	36.50	38.80
3	F2	32.40	36.20	29.40	31.30
4	F3	29.70	32.40	26.60	26.40

Conclusion:
The scope of work focused on the formulation and evaluation of herbal suppositories containing guggul for the treatment of piles. For preparing the formulation extracts of guggul, tridax procumbans, and haritaki were used. Prepared suppositories were evaluated by using different parameters like visual appearance, length and width, melting point, disintegration time, and in vitro anti-inflammatory activity by protein denaturation and protein inhibitory methods. The suppositories comprise guggul, haritaki, and tridax procumbans, which are administered through the rectal route for their anti-inflammatory effect, wound healing, and laxative properties. The visual appearance of suppositories was evaluated, which shows no fissuring, no pitting, no blooming, and no exudation of material. The length and width are 1.9–2.2 cm in length and 0.7–0.8 cm in width, respectively. The weight variation was not more than 5%. The melting time of suppositories was between 35-45 minutes at 37 °C. Protein denaturation of suppositories was found to be 41.40% compared to the marketed formulation of Diclofenac sodium (51.30%). Proteinase inhibition assay showed satisfactory results for all the formulations.

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