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Treatment and cure of ulcer by herbal plants having flavonoids as active constituents.

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Abstract

Ulcers are mostly seen as gastrointestinal problem affecting a large number of humans. It is essentially an eruption on the mucus membrane that lines the gastrointestinal tract or can be seen on superficial layer of skin. Ulcers are formed when the natural equilibrium is disrupted by either increased violent variables or decreased mucosal protection factors. Today there are varieties of synthetic drugs to treat ulcers. However, as opposed to natural remedies, these medications are more costly and are likely to cause more side effects. Nature provides a large number of medicines which has all the solutions to human illness. Herbalists and indigenous healers have used plant derived agents to reduce and cure peptic ulcers for centuries. It was seen that flavonoids show crucial role in various diseases. Many more isolated compounds like Rutin, Quercetin, Kaempherol,Silymarin, Nargingin, and so on give notable results as anti-ulcer drugs. In this narrative review, we have comprehensively reviewed the plant sources having flavonoid as active constituent used as antiulcer agents.

Keywords: Flavonoid, Herbal plant, Medicinal use, Ulcer.

INTRODUCTION

Ulcers are eruptions or wounds on mucous membrane or the epidermal layer with loss of inflamed dead tissue. Ulcers are most often located in the gastrointestinal tract, but they can occur anywhere. Individuals can develop a variety of ulcers, including esophageal ulcers, peptic ulcers, mouth ulcers, foot ulcers and genital ulcers. One of these is peptic ulcer, which can be spotted in many individuals. Peptic ulcers are small wounds that form on the mucosa of the esophagus, stomach, or the duodenum which is anastomosed to the stomach.[1]

Gastric ulcers (GU):GU seems to be very prevalent in persons aged over 50 especially in women. The ulcer can still develop even though in some patients where gastric acid output is regular or even reduced. [2]

Duodenal ulcer (DU): DU is more common in younger people. Various studies have noticed that females are more likely to be affected by peptic ulcers as compared to the males.[3]In the upper abdomen, ulcers on both the anterior and posterior walls of the duodenum can cause excruciating pain and a burning sensation.[4].(Fig 1.)

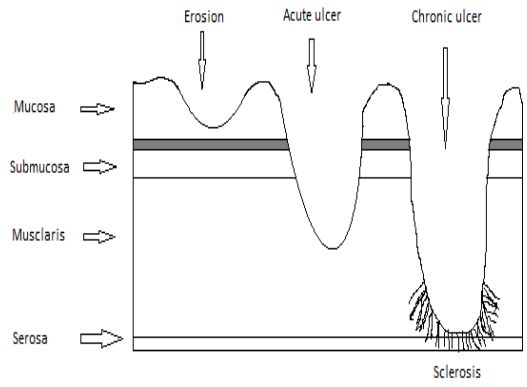

Fig 1. Diagramatic illustrations of acute and chronic gastric mucosal lesion

Now, life can be enervating by peptic ulcers with symptoms like bleeding stool, serious distress in the stomach, and vomiting of blood. Apparently, peptic ulcer disease (PUD) is a non-infectious particularly characterized by repeating symptoms of upper abdominal discomfort, food or alkali generally alleviate them, Apart from this it brings more distress to patients, their daily routine also gets convulsed, and also causes mental trauma.[5] Peptic ulcer disease is caused by a mismatch between violent variable (e.g.,HCl, pepsin) and helpful mucosa-protective variable (e.g. Mucus, bicarbonate barrier, prostaglandin and adequate blood flow), according to studies.[6]Primarily the destructive action of gastric acid and pepsin on the mucosa were thought to be the root behind occurrence of all ulcers in the upper gastrointestinal tract. Although the term "peptic ulcer" has recently been linked to *Helicobacter pylori* infection, emotional stress, alcohol intake and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs[7]. In USA, prescribed NSAIDs have been counterproductive and it is accountable for about 25% of all unpleasant and harmful drug reactions. Every year Approximately 16500 arthritis patients lose their life from gastrointestinal toxicity. [8]Duodenal and gastric ulcer conditions are linked to the *Helicobacter pylori* infection. *H.pylori* is found only in the gastric epithelium, in which the organism tends to cluster around the cell crossroads and seldom penetrates the cell itself. *H.pylori* is not found in blood and is not found in other parts of the body, with rare exceptions.[9]

Antacid and antiulcer drugs account for 6.2 billion rupees in the Indian pharmaceutical industry.[10]Even in this digital age, 75–80percent of the world's population till date relying upon phytomedicines primarily in underdeveloped nation due to finer societal acceptability for primary health care, more suitable, effective for mankind, and fewer after effects.[11]Scintigraphy considered, there was no critical harmless in these natural plant derivatives.

Examination at the initial phytochemical of different herbal plants indicated the existence of chief secondary metabolites such as flavonoids and tannins, areresponsible for antiulcer activity. [12] Currently available in the market include various synthetic antiulcer drugs like proton pump inhibitors, cytoprotective, antacids, anticholinergics, and histamine H_2-blocker utilized commonly to inhibit or treat the various types of ulcers. The high recurrence rate, despite the fact that the ulcer is completely healed, is the major obstacle to the above-mentioned therapy. Moreover, these drugs simplify severe side effects ranging from diarrhea, itching, and dizziness to arrhythmia, impotence, and gynecomastia.[13] When such side effects occur, the condition can deteriorate, lowering the likelihood of a good therapy outcome.This study aimed to assess the herbal plants inAyurvedic resources having flavonoids as active components so as to reveal their potential efficacy and mechanisms of actions**.** The Indian Ayurvedic booklet Materia Medica, as well as electronic databases such as Google scholar, PubMed, science direct, and Scopus, were used to analyses each of the herbal plants.

EPIDEMIOLOGY

Epidemiological investigations have shown that *H.pylori* infection is the major cause of prevalence of PUD, along with it increasing use of NSAIDs. Until the last decades of the twentieth century, PUD had a huge impact on morbidity and mortality. Males have a higher frequency than females before they reach the age of ten. Just 28percent of males were diagnosed before the age of ten, while over 50 percent of females were diagnosed before the age of ten. In reality, peptic ulcers diagnosed in boys account for nearly all of the increase in incidence among 15-year-olds.[14]Despite that environment factor as, in the spring and autumn, the volume and acidity of gastric juice have also been stated to be high. Although some studies from temperate zones support the idea that spring and autumn are the most favorable seasons for the prevalence of PUD, others show a wide range of risk across the year.[15]Several epidemiological studies have accepted that PUD is somewhere related with dyspepsia. The pervasiveness and records of patient with dyspepsia along with peptic ulcer has shown the fact that 50% of seriously dyspeptic men (and approximately one-third of all dyspeptic) have a visible peptic ulcer affirms the severity of their ailment, while the fact that one in ten of these dyspeptics loses his stomach or undergoes some other lifesavingsurgery to treat his ulcer, confirms the complication of their ailment.[16]

Pharmacological agents used in ulcer management

Although the availability of a variety of new effective drugs, pharmacological management of PUD is still evolving, along the objective of focusing care on pain relief, ulcer recovery, and ulcer reappearance prevention. However, many of the pharmacological treatments for PUD are ineffective designed eitherto combat destructive factors or stimulate mucosal protection. Histamine H2-receptor antagonists, Anticholinergics, Antacids, proton pump inhibitors, and prostaglandins are examples of medications used to suppress or neutralize gastric acid secretion.[17] (Table 1)

Table 1. Classification of drugs used as prophylaxis of peptic ulcer. [18-21]

Drug class	Characteristic	Type
Gastric acid secretion Inhibitors. [18]	Decrease gastric acid production, alleviate ulcer pain, promote healing,	H_2 Antihistamine Cimetidine Ranitidine Roxatidine Anticholinergic Oxyphenonium Pirenzepine Proton pump inhibitor Omeprazole Lansoprazole Prostaglandin analogue Misoprostol
Anti H.pylori [19]	Inhibit H.pylori growth, proliferation	Metronidazole Amoxicillin
Antacid [20]	Counterbalance gastric acid	Systemic Sod.citrate Nonsystemic Mag.hydroxide Magaldrate
Ulcer protective[21]	Lessen/halt gastric mucosal impairment	Sucralfate Colloidal bismuth subcitrate

Plant extract with anti-ulcerogenic activity.

The plant extracts with flavonoid and tannin as active constituents were the most frequently analyzed, and were found to have promising cytoprotective, gastric secretion inhibition, anti-inflammatory properties, anti-H. pylori effects, down-regulation of Bax protein, and mucus development improvement.[22]Table 2 narrates the majority of the antiulcerogenic plants as well as their corresponding part used.

Hibiscus rosasinensis.

*Hibiscus rosasinensis*are present in different forms and with several colors of flowers. *Hibiscus rosasinensis L.* (Malvaceae) is a perennial or annual herbaceous bush. It is largely grown in India and origin of this crop is from China, widely known as Chinese rose.[45]Large no. of chemical constituents alkaloid, anthraquinones, tannins, phenols, flavonoids, terpenoids, mucilage, saponins, steroids, essential oils are present in *Hibiscus rosasinensis*.[46]. The *Hibiscus rosa* root (250/500mg/kg) extracted with ethanolic solvent clearly showed gastroprotective activity in albino rats having pylorus-ligated gastric ulcers possibly because it could decrease the secretion of gastric acid in pylorus-ligated rats.[47] Many studies had proved that it can protect the various animal models from ulcers.[48]

Table 2: Plant extracts having antiulcer activity.

S. no	Botanical Name of the plant	Family	Extraction solvent of plant part used	Chemical constituent	Animal used	Ulcer inducer
1	*Asparagus racemosus*[23]	Asparagaceae	Methanolic root extract extract	Flavanoid, shatavarin	Albino rat	Indomethacin
2	*Alstoniascholrs*[24]	Apocyanacea	Ethanolic stem extract	Flavanoids,saponon, steroids, tannin, alkaloids, coumarins	Albino rat	Pylorus ligation
3	*Azadirachtaindica*[25, 26]	Meliaceae	Aqueous extract of leaves	Protein, carbohydrate,flavonoids, and tannins	Rat	Indomethacin, and alcohol
4	*Anacardiumaccidentate*[27]	Anacardiacea	Hydroalcoholic extract of leaves	Catechin	Rat	HCl, ethanol, Pylorus ligation
5.	*Bauhinia purpurae*[28]	Fabaceae	Chloroform leaves extract	Flavonoids, tannins and steroids	Rat	Indomethacin
6.	*Bauhinia variegate*[29]	Fabaceae	Aqueous leaves extract,	Flavonoids	Rat	Aspirin
7.	*Bryophyllum pinnatum*[30]	Crassulaceae	Methanolic leaves extract	Flavonoids	Albino Rats	Pylorus ligation
8.	*Butea foandosa*[31]	Fabaceae	Ethanolic and chloroform leaves extract	Flavonoids, Butrin	Rat	Acid, HCl
9.	*Cynodondactylon*[32]	Poaceae	Alcoholic extract of aerial parts	Flavonoids	Albino Rats	Pylorus ligation
10.	*Eucalyptus maculate*[33]	Myrtaceae	Methanolic leaves extract	Quercetin	Rat	Pylorus ligation, and Cold water immersion
11	*Garlic*[34]	Amaryllidacea e	Aqueous bulb extract	Flavonoids, allicin, allium,	Rat	Cysteamine induce gastric ulcer
12.	*Genistarumelica*[35][36]	Fabaceae	Methanolic Extract of whole plant	Glycoside, Genistin	Rat	Pylorus ligation
13.	*Glycyrrhizaglabra*[37]	Fabaceae	70% v/v ethanol Extract of dried rhizome and roots	Saponon, glycoside, and Flavonoids	Swiss abino mice	Acetic acid, and water immersion
14.	*Hibiscus rosa*[38]	Malvaceae	Methanolic extract of leaves	Anthocyanins, Flavonoids	Rat	Pylorus ligation
15.	*Mangiferaindica*[39]	Anacardiaceae	Ethanolic seed extract	Flavonoids	Female Albino Rat	Acid/alcohol
16.	*Mimosa pudica*[40]	Mimosaceae	Aqueous leaves extract	Flavonoids, tannin and glycoside	Rat	Pylorus ligation
17.	*Moringaoleifera*[41]	Moringaceae	Alcoholic extract of leaves	Kaempferol, quercetin, zeatin, tannin, flavonoids, alkaloids and terpenoid	Rat	Ethanol and Aspirin-induced
18.	*Ocimum sanctum* [42]	Lamiaceae	Alcoholic leaves extract	Flavonoids (apigenin), saponon, tannin, alkaloid	Rat	Ethanol and Aspirin
19	*Rhammusprocubens*[43]	Rhamnaceae	Ethanolic and aqueous extract of whole plant	Kaempherol	Rat	Pylorus ligation
20	*Pycnanthusangolensis*[44]	Myristicaceae	Ethanolic extract of bark	Catechin	Male albino wistar rat	Alcohol

Ficus religiosa.

F. religiosa Linn is from the Moraceae family which is normally known as Peepal.[49] Several studies had highly appreciated various parts of the trees (i.e., leaves, bark, shoot, fruits, latex, and roots) for their remedial property. *F.religiosa* is one of the plants which have been traditionally used to cure gastric ulcer In India.[50].Potential antiulcer activity was demonstrated by ethanol extracts of the bark of *Ficus religiosa* in rats using different ulcer inducer like cold-restrained stress, indomethacin and, pylorus ligation. The reduction of the ulcer index was considered as the determination of the antiulcer effect. The ulcer index got reduced notably when the extract (100, 200 &400 mg/kg) was used in all assay[51] where as another study using leaves extract had shown promising antiulcer effect. The preventive effect had been laid down by the ethanolic leave extract (250 and 500mg/kg) of *F.religiosa* on ulcers using the stress-induced ulcer animal model. [52]

Mangifera indica.

Mangifera indica L. is a luscious stone fruit comes under family Anacardiaceae found mainly in tropical areas it is cultivated widely by farmers in different regions of the world. It is the national tree of Bangladesh , India and the Philippines [53] The other Mangifera species which can be eaten generally have lower quality fruit and are treated as wild mangoes. [54].The extract of ethanol and petroleum ether of leaves was given to albino rats per oral at doses of (250mg/kg) in ulceration model in which Aspirin was used as inducer. As a result, by preventing mast cell development, the extract greatly reduced the negative effects of Aspirin.[55]

Bauhinia purpurae.

One of the well-known plant of Fabaceae family is *Bauhinia purpurae* famous as the camel's foot tree or purple orchid tree. Using different ulcer inducer model like ethanol and indomethacin, the methanolic extract of *B.purpurae* leaf (100, 500, 1000mg/kg) was given orally to the rats. As a result, the extract had substantial cytoprotective efficacy, likely due to an increase in prostaglandin[56]

Mimosa pudica.

Mimosa pudica L. of Mimosaceae family, also known as humble plant is prostrate or semi-erect, a small and medium-sized tree of size approx 1.5 m tall, subherb of America , Australiaand India. The plant is very sensitive soft grey-green leaflets that fold and droop at night and having recurved thorns.[57]Mimosa is one of the largest genera in the legume family, with over 500 species. In Indian conditions, it blooms and bears fruit from August to October.[58]. The antiulcer activity was tested by using pylorus ligation, aspirin, and alcohol models induced gastric ulcers with aqueous extract of the leaves *Mimosa pudica* given at doses of 200 and 400 mg/kg orally. Antisecretory and cytoprotective hypotheses were also investigated. The aqueous extract prevented ulcer development significantly at 200 and 400 mg/kg.

Glycyrrhiza glabra.

Licorice root, reglisse (French), lacrosse (German), and sweet lumber are all common names for it. It is a member of the Fabaceae family and belongs to the genus glycyrrhiza, which has 14 species. It contains amino acids, asparagin, essential oil, glycosides, fat, bitters, estrogen, gums, mucilage, resin, proteins, saponins, starches, steroids, sterols, tannins, flavonoids, volatile oil, and volatile oil.[59].The anti-ulcerogenic activity of *Glycyrrhizaglabra L*. was investigated by hydroalcoholic extract (HEGG) at 50–200mg/kg dose which made a substantial decrease in ulcer index. Along with it, the acetone, aqueous, ethanolic extract of *G. glabra* leaves has been evaluated against micro-organism Helicobacter. Pylori by agar well diffusion method.[60]

Bryophyllum pinnatum.

Bryophyllum pinnatum (Lam.) Kurz.is a succulent herb belongs to family Crassulaceae. It is also called as the leaf of Life or life plant.[61] It has been used as medicine in Africa, India, China, tropical America, and Australia, and grows in tropical, subtropical, and warm temperate climate zones.[62]The plant's leaves have a lot of medicinal value and can be used both internally and externally. Externally, the leaves' pulp or juice is added to traumatic injuries to stop bleeding by contracting the minute arterioles.[63]. Various extracts at doses of 250 and 500mg/kg of extract were evaluated in ethanol induced animal model .As a result this showed significant decrease in free acidity, total acidity and total volume of gastric juice when compared with the control animals.[64]

Allium sativam.

Allium sativum, a species of onion genus Allium member widely known as garlic, is one of the oldest of all cultivated medicinal plants. It belongs to the Amaryllidaceae family. Onion, shallot, and leek are all similar relatives. Garlic grows wild in Central Asia and northern Iran.[65]Allicin, is said to be the main contributors to garlic's distinctive odor, its various decomposition products are diallyl disulfide and diallyl trisulfide.[66].In rats, Garlic juice was given orally at doses of 150 and 300 mg/kg to prevent ulcers which were produced using Aspirin inducer. Improved gastric ulcer healing and reduction in formation of ulcers in stomach and intestine of experimental animals had observed.[67]

Flavonoids as antiulcer agent.

One of the most widely distributed polyphenolic compounds throughout the plant kingdom is flavonoid. Till today about 3000 varieties of flavonoid has been screened.[68] For the maintenance of capillary integrity in mammals, flavonoids are commonly used in medicine.[69]Flavonoids' gastro protective effects have been due to a variety of mechanisms, including an increase in mucosal prostaglandin content,[70] suppression of*Helicobacter pylori* growth,[71]and inhibition of histidine decarboxylase to reduce histamine secretion from mast cells[72]. Free radical scavengers are present in

flavanoid. For ulcerative and erosive bowel diseaseradicals have tremendous effect.[73]. According to the flavylium nucleus, it is comprised of three phenolic rings (A, B, and C) having a basic 15-carbon skeleton (C6-C3-C6).[74]The structural classification of flavonoids is based on benzopyrone saturation and various ring substitutions.[75](Fig 2.) Flavonoids are categorized as flavanones, flavonols, flavonolols,flavones, flavan-3-ols, and isoflavones, Flavonoids are classified into a variety of classes.[76] Table 3

Table 3. Classification of the subclasses of flavonoids based on chemical structure.[73]

Types of Flavonoids	Subtypes of flavonoids	2'	3'	4'	5'	3	5	7
Flavononeс	Naringin	H	H	OH	H	H	OH	O-R
	Naringenin	H	H	OH	H	H	OH	OH
	Eriodictyol	H	OH	OH	H	H	OH	OH
	Hesperidin	H	OH	H	H	H	OH	O-Me
Flavonols	Quercetin	H	OH	OH	H	OH	OH	OH
	Quercetrin	H	OH	OH	H	O-RH	OH	OH
	Rutin	H	OH	OH	H	O-R1	OH	OH
	Kaempferol	H	H	OH	H	OH	OH	OH
	Myricitrin	H	OH	OH	OH	O-Rh	OH	OH
	Galangin	H	OH	H	H	OH	OH	OH
Flavanolols	Silibinin	H	H	O-L-O	H	OH	OH	OH
	Silymarin	H	H	O-L-O	H	OH	OH	OH
	Pinobanksin	H	H	H	H	OH	OH	OH
	Taxifolin	H	OH	OH	OH	OH	OH	OH
Flavones	Rpoifolin	H	H	OH	H	H	OH	O-R
	Diosmin	H	OH	O-Me	H	H	OH	O-R1
	Baicalein	H	H	H	H	H	OH	OH
	Luteolin	H	OH	OH	H	H	OH	OH
	Techtochrysin	H	H	H	H	H	OH	O-Me
	Diosmetin	H	OH	O-Me	H	H	OH	OH
Flavan-3-o1s:	Apigenin	H	H	OH	H	H	OH	OH
	Catechin	H	OH	OH	OH	OH	OH	OH
Isoflavones:	Genistein	H	H	OH	H	-	OH	OH
	Daidzin	H	H	OH	H	-	H	O-Glu

-O-R' = Alkoxy -O-Me = Methoxy -O-L-O = Selane -O-Glu = Glucosyl

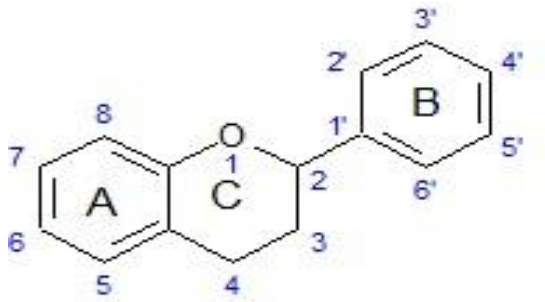

Fig.2 Basic Structure of Flavonoid

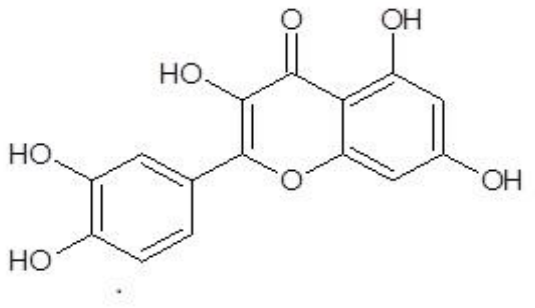

Fig.3 Chemical structure of Quercetin

Quercetin:

Quercetin is an essential bioflavonoid that scientists have widely documented throughout the last 40 years.Flavonoids are widely distributed in nature has phenolic structure that can be seen inroot,bark, fruits, grains, stems, bulbs, wine, and tea.[77]It belongs to the flavonol class of flavonoids and help to obtain many other flavonoids, including citrus flavonoids such as naringenin, rutin, tangeritin, and hesperidins[78] Several studies have shown that Cyclooxygenase activity is stimulated by quercetin. As a result, local prostaglandin output enhancement may be one of the protective mechanisms.[79]Fig 3

Rutin:

Rutin is a one the crucial flavonoid obtained from passion flower, buckwheat, tea, and apple.Chemically it is known as (3,30,40,5,7-pentahydroxyflavone-3-rhamnoglucoside). It's also known as quercetin-3-Orutinoside and vitamin P. Several studies have shown that rutin has cytoprotective effects, includinggastroprotective properties.[80]Rutin is named after the Rutagraveolens plant, which produces rutin as well. Endogenous platelet-activating factor (PAF) may be involved in this flavonoid's cytoprotective impact. PAF mucosal content was inhibited dose-dependently.[81]Fig 4

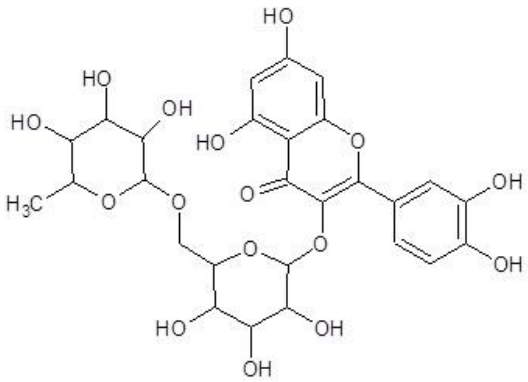

Fig.4 Chemical structure of Rutin.

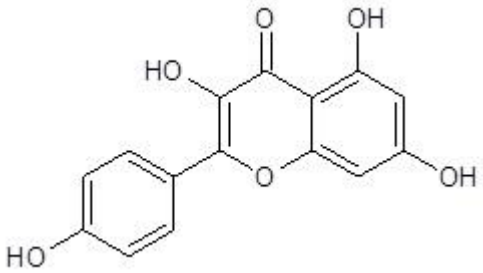

Fig.5 Chemical structure of Kaempferol.

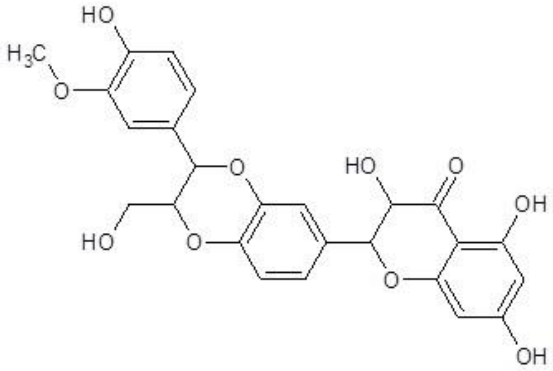

Fig.6 Chemical structure of Silymarin

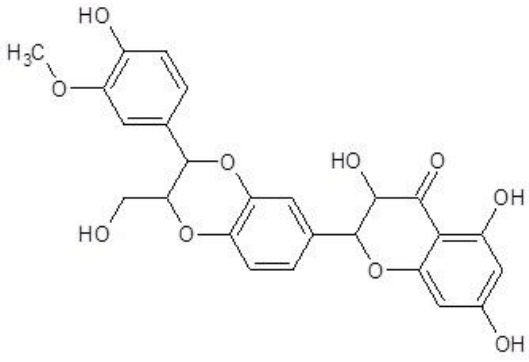

Fig.7 Chemical structure of Naringin

Kaempferol:

It is a yellow compound mostly found in foods obtained from plant origin and traditional medicinal plants.Kaempferol has a low molecular weight (MW: 286.2 g/mol) with chemical name 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-(benzopyran-4-one). The absorption of kaempferol is done by the small intestine. Kaempferol's lipophilicity aids passive diffusion absorption, but various studies proved that active transport or facilitated diffusion may also be used to absorb kaempferol.[82]Fig 5

Silymarin:

Silymarin is a distinctive flavonoid derived from the milk thistle, which contains silybin, silydianin, and silicristin. Recently several studies has proved tremendous role of oxidative free radicals in gastric ulceration animal model induced by cold restraint stress. In rats, silymarin dosage was found to be successful in preventing ulcers in stomach caused by cold restraint stress.[83]Fig 6

Naringin:

Naringinare found in citrus fruits that gives them their bitter taste. It has anti-inflammatory, anticancer, and anti-microbial properties, as well as metabolic syndrome, oxidative stress, bone regeneration effects.[84] In rats, naringin (100 and 200 mg/kg,)administered orally was tested against ulcers induced by ethanol and found to reduce gastric MDA levels, mucosal damage and gastric expression of caspase-3, IL-6with a substantial reduction in mucosal damage.[85]Fig 7

CONCLUSION:

We may infer from this study that plant sources may result in novel and successful treatment of various diseases. The overall results presented in this study demonstrate that herbal plants are a valuable source of important phytochemical with antiulcer potential. Various medicinal plants and extracts (containing active phytochemicals such as tannins and flavonoids) have been shown to have important antiulcer efficacy in animal models in in vivo studies. The flavonoids' antioxidant function is responsible for the majority of their pharmacological effects. Moreover there should be in-depth analysis of the active ingredients. Although traditional procedures have confirmed the clinical effectiveness of these preparations, they have not been clinically tested. While as the prophylaxis of peptic ulcer, several *invivo* evaluation of herbal drugs have shown promising results, only a handful have progressed to clinical trials and even fewer have been under trading. This demonstrates that the valuable research and its results have not been used for whom it is intended, and therefore manpower, money, and time are being wasted. As a result, pharmacologists must devote more time to evaluating herbal drugs for possible antiulcer activity and standardizing effective herbal drugs which would be clinically successful and internationally scientifically validated.

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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