

A review on therapeutic effect of non bio-fermented and bio-fermented product of various herbal drugs in the treatment of gastric ulcer

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ABSTRACT

The plan of this study is to find out the effect of several non Bio-fermented and Bio-fermented product of the various herbal drugs in health promotion. Many traditional medicines were shown to have anti-ulcer activity by using aqueous and non-aqueous solvents and probiotics. Micro-organisms such as *Weissella cibaria*, *Saccharomyces cerevisiae*, *Bifidobacterium*, *Lactobacillus* and *Streptococcus thermophilus* which are already use in bio-fermentation of herbal medicines. Non-steroidal anti-inflammatory drugs have painkiller, anti-inflammatory as well as anti-pyretic properties. These drugs have a side effect of gastric ulcers by inhibition of COX enzymes and reduce the prostaglandin secretion resulting in luminal aggression that induces stomach ulcers. Various Non-steroidal anti-inflammatory drugs inhibit both enzymes COX-1 and COX-2 further categorized as non-selective inhibitors. Stress, eating fast food, consuming more alcohol and busy lifestyles are common causes of gastric ulcers. Probiotics are good for the intestine and stomach because they increase the secretion of prostaglandin (PGE-2) in the mucus membrane, changes the pH of intestine and improve the digestion in the gastro intestinal tract. This study focuses the bio-fermentation of herbal medicines through various microbes. It also suggests that anti-ulcer activity of bio-fermented products is more dynamic than for non bio-fermented products. Here, we suggest that bio-fermented product of herbals shows protective effects in gastric ulcers.

Keywords: *Bio-fermented Product; Herbal Drugs; Non Bio-Fermented Products; NSAIDs; Gastric Ulcer; Probiotic.*

1. INTRODUCTION

An ulcer is a serious problem in the world's population; every tenth person is suffering from stomach ulcer either acute or chronic. [1]. Men are more prone to duodenal ulcer with respect to women [2]. It affects the internal covering of fundus due to excess secretion of HCl which results in damage to mucus and which is similar to open wound [3]. The inflammation of duodenum lining by stomach acid causes an ulcer(s) in gastrointestinal tract [4].

Canker sore, commonly known as mouth ulcers which are visible painful lesions or could be unusual scarred mucus membrane of oral cavity. It is a partial loss of the epithelium in the mouth. Local trauma and aphrodisiac stomatitis are responsible for causing oral ulceration in the buccal mucosa [5]. Ulcers occur within the food pipe that connects the throat to duodenum due to the slow down of mucus secretion is termed as esophageal ulcers [6]. Various factors can cause rupture of the stomach lining, esophagus, and small intestine. Which includes frequent intake of Non-steroidal anti-inflammatory drugs (NSAIDs), *H. pylori* infection, smoking, alcohol intake in excess amount with high frequency, radiation therapy and colon cancer. Through couple of analysis an assumption is unrolled among people that a peptic ulcer is caused due to spicy food, stress and gram-negative bacteria, which deliberately considered to survive within the aggressive atmosphere of the stomach. The peptic ulcers, in general, is diagnosed by observing relative symptoms like change in appetite, nausea, change in color of stool to dark or blood included within, unexpectedly decreased body weight, slower digestive process and vomiting [7]. The receptors are present in parietal cell for acetylcholine (muscarinic), gastrin and histamine.

The receptor-mediated binding of histamine, acetylcholine or gastrin results in the activation of H⁺/K⁺ protein kinases, which in turn stimulates adenosine triphosphate (ATPase) proton pumps that release K⁺/Cl⁻ hydrogen ions it secretes into the lumen instead of the stomach.

Histamine binding causes activation of adenylyl cyclase, while binding of H₂ receptor on the parietal cells which increases the cyclic adenosine monophosphate and then activates the protein kinase that stimulates gastric acid secretion. Improvement of digestive process and increased frequency of muscle contraction within gut caused due to reaction of parietal cell with gastrin. G-cell is responsible for secretion of gastrin a peptide hormone in the inner lining of small intestine [8]. NSAIDs reduce pain, inflammation and regulate body temperature in the event of fever, but they have major side effects such as inhibiting the secretion of prostaglandin, which causes peptic ulcer in the stomach.

Prostaglandin is responsible for stimulation of the secretion of mucus which is protective for ulcer. It enhances their effects by interacting with G-protein coupled prostaglandin receptors. Prostaglandin increases the narrowing of smooth muscles in the stomach as well as increases the secretion of mucus.

By regular use of NSAIDs category drug Indomethacin can damage mucus membrane to cause open wound(s). These kinds of NSAIDs act as non-selective COX inhibitors because they inhibit both cyclooxygenase enzymes isoforms (COX-1 & COX-2) and decrease the prostaglandins secretion in the stomach [9].

2. TREATMENT OF ULCER

2.1. Proton Pump Inhibitors.

Omeprazole, Lansoprazole, Pantoprazole and Esomeprazole.

They are administered as an inactive prodrug. This blocked the stomach acid secretion from parietal cells by inhibiting the proton pump [10].

H₂ Anti-Histamines.

Cimetidine, Ranitidine, and Nizatidine.

These drugs block the histamine receptors on the parietal cell because they inhibit acid secretion. They are less effective than proton pump inhibitors [11].

Prostaglandin analogue.

Misoprostol.

This drug inhibits acid secretion and promotes mucus in the mucosal membrane as well as increase the bicarbonate secretion. This reduced the incidence of NSAIDs induced ulcers [12].

Mucosal protective agents.

Sucralfate.

It is a salt of octasulfated sucrose complexed to aluminium hydroxide. It stimulates the mucosal prostaglandin and bicarbonate secretion [13].

2.2. Anti-ulcer activity shown by non-fermented plant extracts.

Herbal medicines contain active compounds which are good for human health in the treatment of many diseases. However, some drugs are considering less toxic or have lower potency, unlike synthetic drugs. So we can say that herbal medicines are safer as compare to synthetic medicines [14].

Jasminum sambac (Arabian jasmine).

The ethanolic leaf extract of *Jasminum sambac*, promotes the mucus secretion in the stomach due to stimulation of the prostaglandins and protects from gastric ulcer resulting to shows the changes in gastric volume, increase in pH and ulcer index [15].

Honey.

Honey serves gastro protective effect against NSAIDs for induced ulcers; its efficacy depends upon its properties like antioxidant and anti-secretory. They contain active ingredients such as proteins, amino acids, vitamins, enzymes, minerals, flavonoids, organic acid and anti-bacterial components. Also, have cytoprotective action showing protective effects against inflamed kidney due to the use of anti-cancer agents [16].

Aegle marmelos (Indian bael) and *Aloe vera* leaf extract.

Aegle marmelos and *Aloe vera* had utilized gastrointestinal protection with gastric ulcers produced by Indomethacin. Decreased the rate of ulcers with ethanolic extract of *Agale marmalose* leaves was 56.33% compared with the standard group of ulcer medicate Omeprazole (50.44%). This study demonstrates that ethanolic extract of leaves of *Aegle marmelos* and *Aloe vera* has been used for peptic ulcer. *Aegle marmelos* extract contains the chemical constituents are as follows - flavonoids, tannins, and Saponins. *Aloe vera* has few active compounds are aloin, isobarbaloin and emodin [17].

Allium sativum (Garlic).

Garlic is a traditional medicine. The aqueous extract of *Allium sativum* had used in the treatment of gastric ulcer in Wistar albino rat compared with Cimetidine as standard drug. It contains allicin which is responsible for the gastro protective effects. So it proved that garlic extract is better than Cimetidine in the treatment

of gastric and duodenal ulcers [18]. Also utilized methanolic extract of *Allium sativum* for anti-ulcer action against *H. pylori* as results had been showing therapeutic potentials against ulcers [19].

Polyunsaturated fatty acid (PUFAs).

Stomach gastric ulcer is a serious disease and there are many medicines available in the market yet herbal remedy is useful for treating ulcers. The action of this herb inhibits gastric proton pump. ATP_{ase} is progressively successful ways to reduce acid secretion in the stomach and help in healing inflamed lining.

PUFA have similarly effective in oil as compared with Risperine. We can evaluate that PUFA acts as proton pump inhibiting properties that reduce the excess acid secretion by showing an anti-ulcer activity [20].

Mikania scandens (Climbing hempweed).

It acts as a pain reliving and inflammation curing drug. The aqueous and ethanolic extracts of *Mikania scandens* had shown an anti-ulcer activity in rodent because of its components like flavonoids, alkaloids, steroids, saponins, and glycosides [21].

Morinda citrifolia (Indian mulberry).

It is a traditional medicine they had been shown the anti-ulcer activity. In this study ulcer induced by using the ethanol and aspirin through pyloric ligation methods in the animal model then estimate the ulcer index in the treated Wistar albino rats and results have been demonstrated that fruit extract of *Morinda citrifolia* have anti-ulcer property due to its cytoprotective action [22].

Gallarhois (Nutmeg).

Nutmeg contains flavonoids and phenolic compounds. Research concluded that the extract of *Gallarhios* can treat ulcer by decreasing the amount of interleukin-1B, interleukin-6 and cyclooxygenase-2 (COX-2) which usually rise in level by ethanol and HCl. This medication is acting as gastro protective against gastric ulcers [23].

Nigella sativa (Black cumin).

Nigella sativa indicates similar anti-ulcer activity relative to standard drug famotidine against ulcer induced by indomethacin. This herbal medicine had been showing changes in gastric juice volume, pH, acid secretion, and open wound due to inhibition of acid secretion in stomach. They have antioxidant and anti-secretory properties [24].

Brucea javanica (Kosam).

Brucea javanica is contains anti-inflammatory properties as well as antioxidants and also promotes mucus secretion in stomach to shows the gastro protective's effect [25].

Asparagus racemosus (Shatavari).

Several herbal plants and their parts (roots, rhizome, bark, and leaves) are used for the treatment of ulcers. In silico studies, the plant component indicated the secondary metabolites of asparagus racemosus is proteodosin and all residues of interferon- γ during molecular docking then obtained binding energy [26].

Anvillea garcinii.

Anvillea garcinii have to show synergistic effect of its active components such as kaempferol 3-O-rutinoside, quercetin are flavonoids present in ethanolic extract of *Anvillea garcinii* leaves which is responsible for anti-ulcer activity [27].

Tinospora cordifolia (Giloy)

Tinospora cordifolia is very useful as anti-ulcer activity. It's resulting reduces the ulcer index, excess gastric secretion and total acidity. It shows anti-ulcer activity in ethanolic and aqueous extract form. It is a popular conventional medicine which is use in various types of diseases [28].

Citrus medica (Citron).

This *Citrus medica* fruit extract has antioxidant properties because it contains active ingredients such as flavonoids, phenolic compounds, amino acids, proteins and carbohydrates. The result suggests that reduction in ulcer development in histopathological reports proved that citrus fruit had been shown good anti-ulcer activity [29].

Citrus limon (Lemon).

Lemon is effective on gastric issues as well on duodenal ulcers with respect to conventional anti-ulcer drugs Pantoprazole and ranitidine. The research conducted upon several ulcer models variants distinguished on basis of their induced method is acetic acid (chronic), pylorus ligation, ethanol, stress induced, Indomethacin and cysteamine (duodenal) using two different doses to simulate with antiulcer agents. The estimated biochemical parameters measure the ulcer index in all these models includes. In pylorus ligated rats, lemon juice indicates gastric anti-triggered and anti-ulcer effect relatively lemon juice enacts ulcer healing effect up to margin also demonstrates healing of induced chronic gastric ulcers by Pantoprazole and ranitidine in acetic acid. Antiulcer effect of both doses of juice recorded against ethanol, stress and Indomethacin induced gastric ulcers. The duodenal ulcer is induced by cysteamine and is cured by regular use of lemon juice. Anti-ulcer activity which is dose dependent raise the anti-ulcer effects of lemon fruit extract as compared standard drugs such as Pantoprazole and ranitidine [30]. The *H. pylori* infection causes gastric carcinoma and peptic ulcer. Some active ingredients are present in citrus species which is responsible for the treatment of gastric ulcers because it stimulates the prostaglandin secretion in the stomach and inhibits the excess secretion of HCl due to antioxidant properties. In this evaluation, we can evaluate modern

day information in the effects of citrus derivatives as antagonists of *H. pylori* and NSAIDS [31].

Oryza sativa (Rice bran).

The extract of rice bran have an active ingredient like gamma oryzanol to shows gastro protective effects against gastric ulcers resulting in reduced acid secretion and stimulates the production of prostaglandins that protect the mucus membrane [32].

Carica papaya seed.

Carica papaya seed in its extracted formulation shows self-protective effect on mucosal membrane of gastric against ulcer induction by ethanol. *Carica papaya* seed gave therapeutic effect by healing the gastro issues [33].

Curcuma longa.

Curcuma longa extract has an anti-ulcer property. The study revealed that alcoholic extracts possess protective properties against ulcer even many previous studies noted its influential anti-inflammatory activity. NSAIDs and corticosteroids generally used as anti-inflammatory agents. On regular consumption of COX-2 inhibitors altogether with NSAIDs and corticosteroids, gastric ulceration and serious irritation in gut can be experienced which is considered as exception case. Instead of prevalent NSAIDs and glucocorticoids *Curcuma longa* extract considered as optimal alternative. Mechanism of action will be precisely estimated during forthcoming additional studies [34].

Watermelon.

In study, experiment is conducted on animal model to analyze the watermelon seed and rind holds gastro-protective and anti-ulcerative parameters in the gut. The exceptional markdown in mean ulcer score recorded in this study of watermelon on its property of anti-gastric acid secretion. It scales down the maturing of ulcers in comparison to reference drug Ranitidine. Watermelon extracts greatly influenced NO synthesis on anti-ulcer activity due to consisting citrulline and flavonoids in high percentage while representing anti-secretory and anti-oxidant effects. In traditional medication processing, watermelon is seed and rind used frequently which is remarkable. [35].

3. FERMENTATION

The procedure that conducted for identification of microbes is termed as Microbial fermentation; also used in pharmaceutical industries and processing food items. Mass culture of micro-organisms carried out using either aerobic process or anaerobic process. Whenever a biological procedure occurred in lack of oxygen results in rotten food [36].

3.1. Mechanism of Fermentation.

Glycolysis process continued by the formation of NADH from NAD⁺ once accepted a final electron during fermentation in which an organic molecule used. As glycolysis processed, the amount of ATP generation is very low i.e. just twice for each molecule of glucose by fermenters. While in fermentation no ATP produced as it does not include transportation of electrons in its system. In fermentation of lactic acid, pyruvate reduces to lactic acid itself by obtaining electrons from NADH. In homo-lactic fermentation, microbes form lactic acid. Gastrointestinal tract's health maintained by lactic acid produced by intestinal microbial flora that also restrains the pathogens develops in definite body regions [37]. The production of beverages containing alcohol

within, baked edible products and even production of bio-fuels contains ethanol fermentation in their pipelined process. To emphasize different flavors in edible items several fermentation methods implemented, propionic acid fermentation is one among. Some microbes purposely categorized based upon fermenting approaches and yielded products which can also be further differentiated on type of substrate it ferment [38].

3.2. Importance of Fermentation.

Fermented foods are beneficial to human health and many types of probiotics micro-organisms such as bacteria, yeast, and molds used in the fermentation process in various products and by-products. The substrate used to transport and distribute probiotics can increase enzyme activity which is beneficial for human health [39]. Probiotics are more effective for a healthy digestive system. It can increase the mucosal secretion in the stomach and protect it from the peptic ulcer. Besides, it supports the absorption of nutrients and contributes to a healthy immune response. The mechanism process performed on gastrointestinal diseases also shows defensive action on gastric mucus obstruction while

regulating certain parameters such as prostaglandin, mucus, growth factor, anti-inflammatory and cytokines [40].

3.3. Anti-ulcer activity shown by Bio-fermented plant extracts.

Fermented Barley Extract with Ethanol model.

Analyzed in mice that barley, in its fermented form helps in reduction of inflamed gastric mucosal which is occurred in reaction of HCl and ethanol mixture. The effective results are achievable by using *Weissella cibaria* and *Saccharomyces cerevisiae*. So, it can be useful to treat patients suffering from gastric mucosa disorder as a regular food supplement [41].

Fermented Barley Extract with NSAIDs model.

Analyzed protective effects on rats (*Sprague-Dawley*) evaluated by certain parameters. Oral fermented barley extract given at (100/200/300) mg·kg⁻¹ strengthens anti-oxidants level and anti-inflammatory system against gastric mucosal damage caused by induction of Indomethacin. The above mentioned dose amount of fermented barley extract can help to recover a different level of gastric damages. The experiment on rats shows significant improvement in Indomethacin induced gastric damages at dosage of 100 mg·kg⁻¹ [42].

Broccoli sprouts extract (BSE) and yogurt.

In research, neither *B. bifidum* nor *Lactobacillus acidophilus* reported any of the inhibitory effects by extracted broccoli sprout. The acidity was less in standard group with respect to control group because the elevated Broccoli sprouts extract level in yogurt is responsible for increment in concentration of Broccoli sprouts extract and its product altogether. Yogurt's shelf-life preserved little longer duration than usual using broccoli extract as it elevates in yogurt's acidity which acts as preserving agent. This study shows an anti-ulcer effect of BSE. Increment in Broccoli sprouts extracts concentration is directly proportional to the number of probiotics bacteria in considered samples. The composite effect of BSE and probiotics bacteria analyzed during the study for the growth inhibition of *H. pylori* [43].

Fermented milk.

Streptococcus thermophilus, lactic acid bacteria strain by fermented milk which holds the capacity of exopolysaccharides polymers which are responsible to protect the mucus and gastro protective effects in reduction of the open lesion against gastric ulcer induced by acetic salicylic acid. [44].

Fermented Soybean.

Soybean, also known as *Shuidouchi* is a conventional food. In fermented form, it shows distinct defensive effect on animal model using *in vivo* method for colitis. During experiment, it's analyzed by serum and mice's colon tissue that the *Shuidouchi* found inhibiting colitis effect and alleviate colitis, also normalizing indexes to normal state of mice body Simultaneously, the active components of fermented soybean have reliable effect as compared with the protective effect of colitis. It is the most popular food by which colitis inhibited as it is very useful during new development and medication utility [45].

Fermented lotus root (FL).

The Fermented bio-product of Lotus root is beneficial for gastric problem analyzed by determination of antioxidant activity and inflammation by inhibiting the nuclear factor kappa-B signaling pathway in mucosa ruptured by ethanol and HCl induced model. Bio-product of FL also has therapeutic properties by which

antioxidant reactant altogether with anti-inflammatory composing heredity chromosome moderated [46].

Fermented Rice Extract (FRE).

While studying effects of Fermented rice extracts probiotics with bacteria *Saccharomyces Cerevisiae* and *Weissella Cibaria* during the process of 'triple' fermentation proved commendable denoting its therapeutic possibilities for Ulcerative Colitis.

UC is a disease caused due to inflammation in bowel (colon) tract considered chronic which is signaled by the ulceration caused in gut mucosal also termed as Inflammatory Bowel Disease. UC model of mice medicated orally by sulfasalazine or Fermented rice extract at dose of 300/200/100 mg·kg⁻¹ to cure the inflammatory bowel disease once a day during a week, induced by Dextran Sodium Sulfate. In the mean duration control group kept on distilled water. In test group colonic shortening, decreased body weight and blood passing within stools observed. Although, distinctively Fermented rice extract at dose of 300 mg·kg⁻¹ resulted as weight loss reduction, ulcer index score of disease is mark down, promotes colon weight decrement and colorectal length is increased. Analysis report of histopathology acknowledged mild differences occurred in the colonic cells (tissues) and about damaged mucosal in the Fermented rice extract group collectively with constrained inflammation. The report showed that Fermented rice extract potentially improves UC by deflation of microbiota in the Fermented rice extract groups and elevation in numbers of beneficial bacteria like *Lactobacilli* and *Bifido*. The lipid peroxidation downsized while antioxidant activity is intensified [47].

Wheat-Germ-Apple Fermented (WGAF).

Experiment of Ulcerative colitis model on mice came out with enormous deterrent effects by formulated product of probiotic culture when mixed with Alcoholic-WGAF, which is extracted using alcohol and appropriate juice proportions of apple with wheat germ. Several symptoms found alleviated in mice when colitis induced using Dextran sodium sulfate like pilling up the number of specific nutrients, diminishing of experienced oxidative force by mice in colon tissues, suppressing the stimulation of the nuclear factor kappa B-cell, balancing out ulcerative colitis relevant inflammatory influencers and soothing the endocytosis of epithelial cells in intestinal which was observed before mechanism of Alcoholic-WGAF. This solidifies the present components of wheat germ and apple with its mechanism at molecular level by explaining how it contains elements such as polyphenols, flavonoids, antioxidant peptides, unsaturated fatty acids etc. The ethanolic extract of wheat germ apple fermented increased the antioxidant activity which gives ulcerative colitis treatment [48].

Black Tea (BT) and Kombucha Tea (KT).

Black Tea (BT) as herbal medicine versus fermented product of BT with *Candida parasilosis* and Kambucha named as CT and KT respectively. Study on mice model is to compare the effect of both non-fermented and fermented products used to cure stomach ulcers induced by Indomethacin. The healing ability of BT herbal product noted during an experiment to reduce ulceration. While the kombucha culture boosted the when fermented but not in when fermented formulation constitutes *Candida parapsilosis*.

The KT4 sample, formed by fermenting KT for about four days which turns out in having enough potential to scavenge DPPH

radicals and phenolic contents. The KT4 (fermented tea formulation) at dose of 15 mg/kg holds almost equal potential with respect to Omeprazole at dose of 3 mg/kg to heal ulcer(s) in positive group of mice model. When comparing the activity of KT4, CT4 and BT for ulcer healing of KT4 revealed more promising results. The antioxidant in KT4 prevents the rupture of mucous membrane which supports as shield during the gastric reactions. All the formulated extracts of tea at dose of 15 mg kg⁻¹ could sufficiently heal the ulceration as unfold in histopathological and biomedical studies. The relative efficacy is noted as KT4 > CT4 > BT. So Kombucha tea (KT4) is more effective than extract of black tea (BT) in the treatment of ulcer [49].

3.4. Correlation between non Bio-fermented product and Bio-fermented product of herbal drugs for anti-ulcer activity.

4. CONCLUSIONS

This study indicates that bio-fermented product is more beneficial relative to non bio-fermented product of herbal medicines. The number of fermented product used as medication in several diseases. Some medicinal herbs, which do shows anti-ulcer activity are ferment by using probiotics microbes such as *Lactobacillus*, *Bifidobacterium*, *Weissella cibaria*, *Streptococcus thermophilus* and *Saccharomyces cerevisiae*. Mechanism includes:

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Numbers of researchers have been proved that fermented product is more beneficial in various diseases as compared to non-fermented ones. Fermented Products containing the micro-organism which includes bacteria are called probiotics. Probiotics are the bacteria contained in fermented edible serving health benefits that can survive up to thousands of years. It aids the digestion by pre-absorption of anti-nutritional component which increased feed ability and inhibiting intestinal disorders. They are utilized for production of various types of protease like alkaline protease and high-temperature protease also pectinase, esterase, lipase, amylase, lingninplum and cellulose. Due to the presence of probiotics in fermented product the activity is increased [50].

activation of the immune cells results in increase mucosal immunity, improves the epithelial barrier, inhibit the inflammatory factors or NF-kB signaling pathway and inhibits adhesion of bad pathogens. Bio-fermented products of herbal drugs during demonstration directly or indirectly their efficacy on the mechanisms which is more effective as compared to non bio-fermented product involved in the treatment of gastric ulcers.

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