

# Herbal Remedy: An Alternate Therapy of Nonsteroidal Anti-Inflammatory Drug Induced Gastric Ulcer Healing

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India has immeasurable varieties of tropical plants. Native Indians possess a long tradition of Kabiraji medicine utilizing such medicinal plants. The Indian Medicine Central Council Act 1970 recognizes Ayurvedic medicine. The World Health Organization also sponsors and encourages research in Ayurvedic treatments<sup>1</sup>. The use of herbal medicine can be traced back to China about 5000 years ago. Extracts of several plants have been used as therapeutic agents for many diseases by virtue of their antioxidant actions. Spices and herbs are recognized sources of natural antioxidants, many of which are phenols and aromatic amines. These can act at different levels by decreasing local oxygen concentrations, decreasing superoxide formation, preventing chain initiation, metal-induced free radical generation, and lipid peroxidation. However, despite the large varieties of such plants grown in India, a minimal number has been thoroughly studied for all aspects of their potential therapeutic value in medicine. A growing body of evidence suggests that at least part of the therapeutic values may be contributed by their antioxidative property. These natural antioxidants may therefore contribute to protect the human body from several diseases<sup>2</sup> including gastric ulcer.

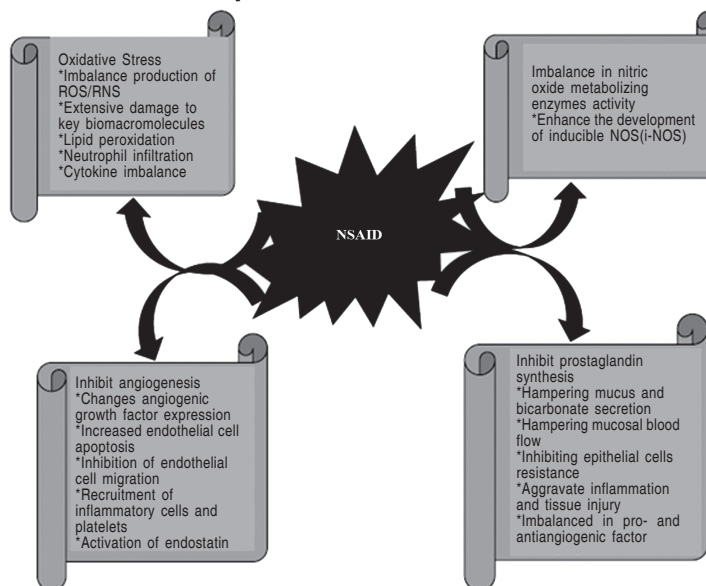
Clinical research has confirmed the efficacy of several medicinal plants for the treatment of gastric disorders, and basic scientific research has uncovered many of the mechanisms to explain their therapeutic effects<sup>3, 4</sup>.

Gastric ulcer is a common disease, where the gastric mucosa gets damaged and perforations lead to bleeding. A report of the Indian Council of Medical Research on the epidemiology of gastric ulcer in India showed that the overall prevalence rate of the disease ranged from 1 to 6.5 per thousand in the age group of 15 years and above in a selected urban population. Mahadeva and Goh have extensively studied and reported the epidemiology of this disease<sup>5</sup>.

A number of factors are responsible for this gastric ulcer

disease of which 70% to 80% are due to infection of *Helicobacter pylori*, a spiral shaped, gram negative bacteria<sup>6-8</sup>. However, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) accounts for approximately 25% of gastric ulcer cases with an upward trend<sup>9</sup>. The NSAIDs are one of the most widely prescribed drugs in the world and are extensively used to alleviate clinical cases especially for pain and inflammation<sup>10</sup>. However, these drugs are well-known to induce stomach ulceration and delay ulcer healing<sup>11</sup>. Despite recent advances, an adequate remedy for the NSAID induced gastropathy remains elusive. The World Health Organization has stressed the need to develop drugs from plant origin, which will be inexpensive, accessible particularly to the rural people in

**Figure 1 : Schematic presentation of mode of action of NSAIDs**



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the developing countries, and show less/no side effects. Therefore, development of a drug having antiulcerogenic property from plant sources without compromising the efficacy and safety would be expected to benefit millions of suffering humanity.

### 1. Antiulcer Drugs of Herbal Origin

The herbal and other indigenous sources have not adequately been explored for the presence of safe and effective antiulcer drugs. Though certain plants and their purified constituents have been reported to possess significant antiulcer potential during the last three decades, the studies have not been carried forward to a logical conclusion for establishing their clinical usefulness as has been done for various modern drugs like H<sub>2</sub> receptor antagonists and proton pump inhibitors. An attempt has therefore been made to summarize some important studies on the antiulcer potential of herbal drugs which may provide some clues in undertaking this challenging task of finding out a safe and promising drug from natural sources. This review includes the studies of some of plants which have a beneficial role against NSAID induced gastric ulceration and are listed as follows.

1.1. **Anthocyanosides.** Anthocyanosides, obtained from *Vaccinium myrtillus*, exert a significant preventive and curative antiulcer activity. It influences biosynthesis of the mucopolysaccharides, thus improving the efficiency of the mucus barrier at the gastric level<sup>12, 13</sup>.

1.2. ***Apium graveolens.*** It is a plant species in the family Apiaceae commonly known as celery. An ethanol extract of celery is also used as a drug against gastric ulcer on rats. It

was shown by Al-Howiriny et al., at the dose of 250 and 500mg/kg body weight, that ethanolic extract of celery showed antigastric ulcer activity against indomethacin, cytodestructive agents (80% ethanol, 0.2M NaOH, and 25% NaCl), and cold restraint stress induced ulceration on rats.

*Apium graveolens* extract significantly protects the gastric mucosa and suppresses the basal gastric secretion in rats, through its antioxidant potential<sup>12</sup>. In animals, bilberry decreased the incidence and severity of experimentally induced ulcers<sup>13</sup>.

1.3. ***Bupleurum falcatum.*** *B. falcatum* is a species of flowering plant in the Apiaceae family. The roots of *B. falcatum* have been used clinically in Chinese and Japanese herbal medicine (kampo medicine). Shibata et al.<sup>13</sup> have reported that a crude saponin fraction of *B. falcatum* showed weak antiulcerogenic activity in pylorus ligated ulcer model. Yamada et al.<sup>14</sup> found that the polysaccharide fraction of *B. falcatum* possesses potent antiulcer activity against HCl/ethanol induced lesions in mice.

1.4. ***Curcuma longa.*** It is a perennial herb from Zingiberaceae family, distributed native to India and Southeast Asia. It has extensively been used in medicine. Curcumin, an active component of *Curcuma*, shows anti-inflammatory and antioxidant properties. On the basis of its antioxidant property it scavenges reactive oxygen species and regulates MMP activity to exert antiulcer activity<sup>15</sup>. Curcumin (diferuloylmethane), a yellow pigment in turmeric *Curcuma longa*, is used widely as a spice in Indian and Thai cuisine. It exhibits a number of pharmacological effects including anti-inflammatory activity, induced by suppression of PG

synthesis<sup>16</sup>. Turmeric root extract has been found to relieve pain from biliary dyskinesia during a double-blinded study<sup>17</sup> and improve endoscopic healing of peptic ulcers as well as symptoms of patients with nonulcer dyspepsia<sup>17</sup>. There is currently much interest in its potential as a selective COX-2 inhibitory agent<sup>18</sup>.

1.5. ***Camellia sinensis.*** It is the most popular nonalcoholic beverage worldwide. Extensive work has been carried out regarding various medicinal attributes of green tea. The prophylactic action of the tea seed derived triterpene saponins against ethanol-induced gastric mucosal lesions<sup>19, 20</sup> and black tea extract against various ulcerogens<sup>21, 22</sup> has been reported in rat models. Theaflavin (TF) is a major active component of black tea. TF healed indomethacin induced gastric ulcer by its antioxidative properties, synthesis of PGE<sub>2</sub> and enhancement of mucin secretion. TF also helps to suppress various inflammatory modulators in ulcer margin<sup>23</sup>. eNOS modulation may be another possible pathway of gastric ulcer healing by TF<sup>23</sup>.

1.6. ***Glycyrrhiza glabra.*** Liquorice or licorice is the root of *Glycyrrhiza glabra* from which a somewhat sweet flavour can be extracted. The liquorice plant is a legume (related to beans and peas) that is native to southern Europe and parts of Asia. It is placed under the family Fabaceae. It is a herbaceous perennial, growing to 1m in height. In north India it is known as "Mulaithi." The root of *G. glabra* is known as licorice used for the treatment of gastric ulcer in Europe. It had been reported that licorice derived compounds elevate the prostaglandin level and promote the mucus secretion from the stomach, increase the life span of surface cell of

stomach, and had an antipepsin activity which ultimately leads to ulcer healing<sup>23</sup>. Extracts of licorice have demonstrated the ability to accelerate the healing of gastrointestinal ulceration (especially in the stomach and esophagus) possibly due to its antioxidant effect. The antiulcer drug carbenoxolone, a succinate derivative of glycyrrhetic acid, was developed in London in the early 1960s and has become the preferred form of licorice used to promote healing of ulcers<sup>22</sup>.

**1.7. *Kochia scoparia*.** Saponins isolated from the fruit of *Kochia scoparia* have been demonstrated to possess gastroprotective properties<sup>22</sup>. Its gastroprotective action is believed to be via activation of mucous membrane protective factors rather than inhibition of gastric acid secretion.

**1.8. *Lagenaria vulgaris*.** *Lagenaria vulgaris* is a popular vegetable, placed under the family Cucurbitaceae. This plant shows antiulcer activity through an antioxidative pathway by modulation of glutathione level<sup>20</sup>. In India, like other parts of the world, market available medicines are widely used for the prevention of different diseases, like inflammation, hypertension, pain sensation, gastritis, cancer, and so forth. But long term use of such synthetic medicines ultimately causes gastroduodenal risks. So, there is a growing need to find naturally synthesized plant based medicines which are devoid of this side effect. The healing potential of the plants is due to their ability to synthesize the aromatic substances such as phenols and flavonoids, which serves as defense mechanism against different diseases. These substances scavenge the free radicals generated on administration of NSAIDs and

increase the cellular defense activity. The nonsteroidal anti-inflammatory drugs exert both their therapeutic and toxic effects mainly through the control of the activity of cyclooxygenase. But long term use of such painkillers inhibits the cyclooxygenases (COX) activity and decreases the levels of circulating prostaglandin (PG) at the gastric mucosa causing gastric ulceration and also exacerbating preexisting gastric ulcers in rodents and humans<sup>20</sup>.

The antiulcerogenic potential of the natural polyphenols (drugs) could be attributed to their divergent effects on angiogenesis. Gastric ulcer healing is a complex process involving angiogenesis and cell proliferation. All these eventually help in wound retraction and reepithelization by regulation of proangiogenic factors as well as antiangiogenic factors. Clinical and other experimental data consider the role of angiogenesis during NSAID induced gastropathy; the effect of the plant drugs may augment the growth of new blood vessels and decrease their ulcer healing action.

So, addition of nutraceuticals in daily habit is the alternate therapy to protect from different diseases by preventing oxidative stress and improving the stores of critical elements such as antioxidants, vitamins, and so forth.

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