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Review Article

# Biotechnological aspects of plants metabolites in the treatment of ulcer: A new prospective

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ABSTRACT

Ulcer is one of the most common diseases affecting throughout the world population. The allopathic treatment of ulcer adversely affects the health by causing harmful side effects. Currently, many herbal plants and secondary metabolites have been used for the ulcer treatment. In the present review, many herbal plants and their parts (root, rhizome, bark, leaves and fruits) have been listed in the table are currently being used for ulcer treatment. These metabolites are responsible for ulcer-neutralization or anti-inflammatory properties. In silico study, plant metabolites showed interaction between protodioscin (secondary metabolites of *Asparagus racemosus*) and interferon-γ (virulent factor of gastric ulcer) during molecular docking. All the residues of interferon-γ exhibited hydrophobic interactions with plant metabolites. These interactions helps in understanding the plant secondary metabolites *vis a vis* will open a new door in the research field of new drug discovery and designing for the ulcer treatment.


**Contents**



## 1. Introduction

Plants and their secondary metabolites have been used as one of the important sources in the field of medicines or health related issues since ancient times. The role of medicinal plants in the health care had been already mentioned in the Indian holy books like “Vedas” [1]. Recent report of World Health Organization (WHO) has been estimated that approx 45,000 plants being practiced for the medicinal purposes across the globe [2]. Presently, around 65% of Indian population directly are dependent upon the traditional medicine for their need of primary health [3]. Secondary metabolites of these herbal plants is an alternative source broadly used in the treatment of chronic diseases [4]. Currently, traditional medicine is broadly

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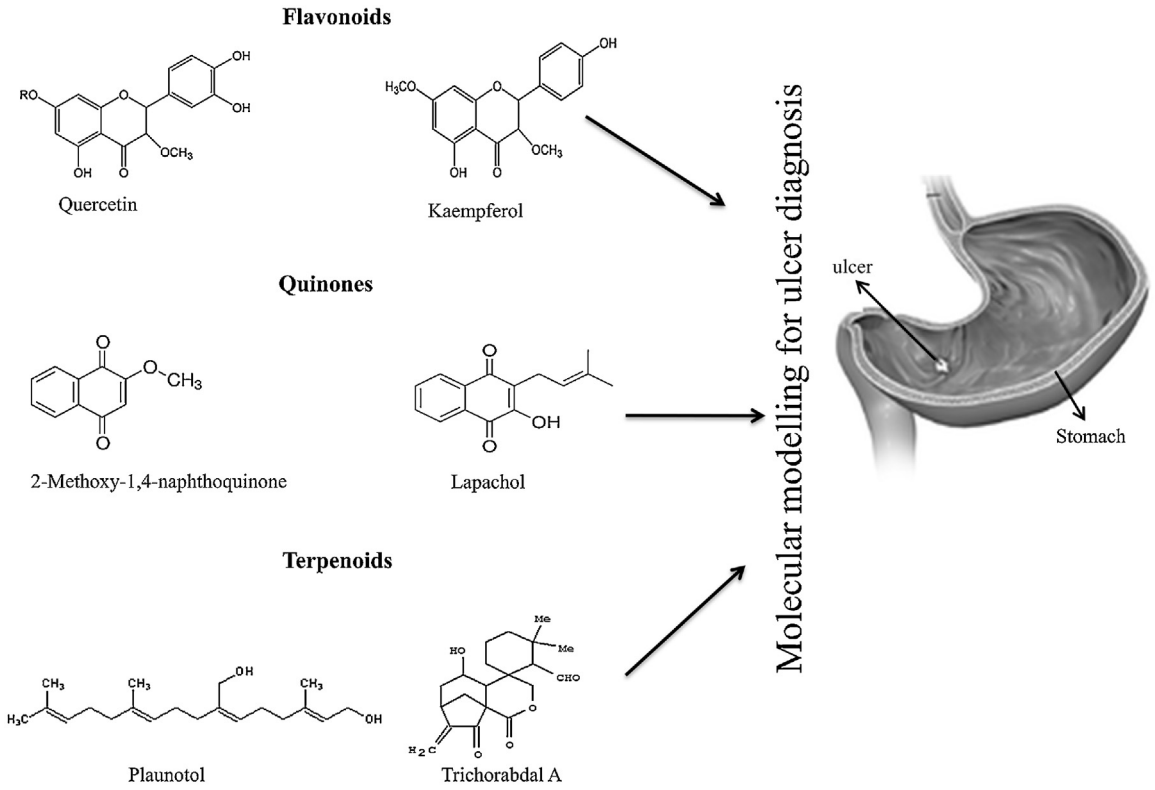


**Fig. 1.** Overview of anti-ulcer metabolites from plant.

used in the treatment of ulcer worldwide, and has been proven as one of the best strategies for the disease management of ulcer (Fig.1).

Ulcer is a discontinuity or break in a bodily membrane in the form of wound or sores that are slow healing or keep returning. It impedes the organ of which that membrane is a part from continuing its normal functions (https://en.wikipedia.org/wiki/Ulcer). It is of many forms which occur on both, inside and outside of the human body. Currently, different types of ulcer forms are recognized in medicine such as peptic ulcer, corneal ulcer, stomach ulcer, foot or leg ulcer *etc*.

Ulcer causing problems in digestive system and wounds appearing in the lining of digestive track in human beings are very common. The digestive track of human beings is very sensitive and the health of digestive track can be good or bad and depends on many factors. Pepsin exposed ulcers *i.e.*, peptic Ulcers are the most common type in the gastrointestinal tract area that result from an imbalance between stomach acid-pepsin and mucosal defence barriers and more than 4 million people affected worldwide annually [5,6].

In medicine, the ulcer which occurs as mucosal lesions which penetrate the muscularis mucosae layer and form a cavity surrounded by acute and chronic inflammation is defined as peptic ulcer [7].

Peptic Ulcers can be divided into two common types according to location, *i.e.* gastric ulcer (in stomach) and duodenal ulcer (in duodenum). More specific classification includes

1 **Type I:** Ulcer along the lesser curve of stomach
2 **Type II:** Two ulcers present - one gastric, one duodenal
3 **Type III:** Prepyloric ulcer
4 **Type IV:** Proximal gastroesophageal ulcer
5 **Type V:** Anywhere

Peptic ulcer disease (PUD) is an illness that affects a considerable number of people worldwide. It is produced whenever there is imbalance between the gastro-duodenal mucosal defence mechanisms *i.e.* 'protective' factor and 'aggressive factor' of the luminal surface of the epithelial cells, combined with superimposed injury from environmental or immunologic agents. The aggressive factors inculde *Helicobacter pylori*, HCl, pepsins, nonsteroidal anti-nflammatory drugs (NSAIDs), bile acids, ischemia, hypoxia, smoking and alcohol [8].

## 2. Symptoms

Inspite of serious bleeding, big ulcer shows some common symptoms (Fig. 2) while small ulcers rarely or mayn't cause any symptoms [9].

## 3. Treatments

Earlier there were mainly two ways for the treatment of the peptic ulcer, the prophylactic and therapeutic types.

### *3.1. Prophylactic mechanism (gastroprotective or cytoprotective)*

In this type of treatment, defensive factors are fortified with strengthened prostaglandin synthesis and stimulated somatostatin synthesis in addition with other gastroprotective actions inhibition of gastrin secretion [10–12].

In addition, oxidative damage prevention of gastric mucosa (by blocking lipid peroxidation and significant decrease in superoxide dismutase along with increase in catalase activity) ([13,14]), possible participation of the NO-synthase pathway [15] and anti-inflammatory activities are several others gastroprotective effects which helps in the treatment of the peptic ulcers.

### 3.2. Therapeutic mechanism

Therapeutic agents cure the diseases *via.* antisecreatory or healing activities. Antisecreatory activity has the antagonism of histaminergic and cholinergic effects on gastric secretion or proton pump inhibition mechanism while healing activity works by making ulcer to heal by local mucosal enhancement.

### 3.3. Synthetic drugs

There is a plethora of different classes of pharmacological drugs that showed their efficacy in the treatment of peptic ulcer. Besides their novel cause, they could also destroy a person's life by causing a general deterioration of quality of life along with creating several other life hazards. Synthetic drugs of different classes applied in

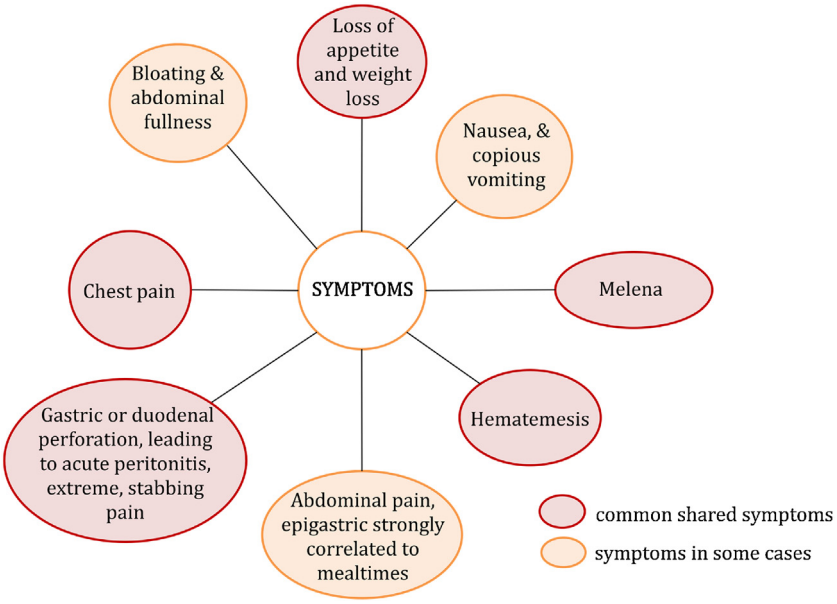


**Fig. 2.** Some common symptoms of ulcer.

**Table 1**
Synthetic drugs applied in the treatment, mode of action (MOA) and their side effects.

| Drug class | MOA | Medicine used | Side Effects |
|---|---|---|---|
| **Anti-Muscarinie** | • Blocks M1 muscarinic receptor<br>• Dec. vagal stimulation<br>• Inhibits gastric secretion<br>• Dec. pepsin secretion | Pirenzepine | • Dry mouth<br>• Blurred Vision<br>• Tachycardia<br>• Photobia |
| **$H_2$-receptor blockers** | • Inhibitor of $H_2$ receptor (CYP450) | Cimetidine, Famotidine, Ranitidine | • Headaches,<br>• Myalgia<br>• Diarrhea,<br>• Renal impairment,<br>• Confusion |
| **Prostaglandins** | • Inhibits the acid secretion<br>• Promotes mucus and bicarbonate secretion | Misoprostol | • Diarrhea<br>• Abdominal pain<br>• Vomiting and nausea<br>• Headache |
| **Antacids** | • Neutralize the HCl<br>• Reduces pepsin formation | Sodium bicarbonate, Calcium bicarbonate | • Diarrhea<br>• Constipation<br>• Hypokalemia |
| **Proton pump inhibitors** | • Inhibits $H^+/K^+$ ATPase in parietal cells | Omeprazole, Esomeprazole, Pantoprazol | • Risk of Pneumonia<br>• Headaches<br>• Diarrhea<br>• Nausea<br>• Weakness |
| **Mucosal protective agents** | • Forms a protective layer by binding with proteins found in base of the ulcer<br>• Stimulates angiogenesis for healing<br>• Inhibits pepsin activity<br>• Antimicrobial activity against *H. pylori* | Sucralfate, Bismuth Subsalicylate | • Dry mouth<br>• Skin rash<br>• Headaches<br>• Darkening of stools<br>• Severe Constipation |

the treatment with their mechanism of action (MOA) and side effects are given in Table 1.

## 4. Plant and their products with anti-ulcer activity

Natural products exhibit their antiulcerogenic activities *via.* prophylactic or therapeutic or by both ways. Extracts of *Saussurea lappa* C.B. Clarke [16], *Zizyphus oenoplia* (L.) Mill. [17], *Zingiber Officinale* Roscoe [15], *Butea frondosa* (Roxb.) [18], *Anacardium humile* St. Hil. [10], *Lasianthera Africana* P. Beauv. [19], *Gymnosporia rothiana* [20], *Coccinia grandis* Linn. [21] and *Zataria multiflora* Boiss. [22] showed cytoprotective mechanism to treat PUDs. Extracts possessing antioxidant mechanism in the gastroprotection are *Encholirium spectabile* Mart. [13], *Parkia platycephala* Benth. [23], *Glycyrrhiza glabra* L. [24] and C*arica papaya* L. [25].

Therapeutic agents are extracts of *Terminalia chebula* Retz. [26], *Mikania laevigat*a Schultz Bip. [27] and *Pausinystalia macroceras* (K. Schum.) Pierre ex Beille [28]. While plant extracts that perform through healing activity includes *Quassia amara* L. [29], *Matricaria chamomilla* L. [30] and D-002 (mixture of higher aliphatic primary alcohols isolated from beeswax) [31]. Another ways of wound healing mechanisms includes thick coating of the extract (like *Rhizophora mangle* L.) which is macroscopically adherent to the gastric mucosa, forming a physical barrier with similar properties as observed in topical wounds [32].

In addition, there are some plant extracts that exhibit both the prophylactic and therapeutic mechanisms like *Mentha arvensis* L. [33], *Polyalthia longifolia* (Sonn.) Thwaites (PL) [34], *Strychnos potatorum* Linn (Loganiaceae) [35], *Alhagi maurorum* Boiss. [36], *Indigofera truxillensis* Kunth [37], *Syngonanthus bisulcatus* (Koern) Ruhland [38], *Pausinystalia macroceras* (K. Schum.) *Pausinystalia yohimba* Pierre ex Beille [28] (Table 2).

Many researchers studied different plant species and their extracts to analyze their impact on ulcer treatments. Xiao et al. [51] during his study reported significant impact of *Abrus cantoniensis* ethanolic extract on the growth inhibition of *Helicobacter pylori*. The actual mechanism of action was not studied but they observed *Abrus cantoniensis* as a rich source of saponins, anthraquinones, alkaloids, flavonoids *etc*. The secondary metabolites present in the plants may act as anti-*Helicobacter pylori* substances since some metabolites analogues to the well-known anti-*Helicobacter pylori* compounds like cabreuvin, irisolidone, genistein and licoisoflavone [52–54] (Table 3).

*Saussurea lappa* is also a traditional medicinal plant having anti-*Helicobacter pylori* properties. This plant also has a rich source of sesquiterpenes, monoterpenes, triterpenes, aromatic compounds, sterols, alkaloid [55,56]. Besides raw plant products or extracts, volatile oils of the plants also play a significant role in the inhibition of ulcer [57]. Many researchers reported different plants volatiles oil having singnificant role in anti-*Helicobacter pylori* like

**Table 2**
Plants and their mode of action in ulcer treatment.

| Plant | Family | Dose applied ($mg\ kg^{-1}$) | Mode of Action | References |
|---|---|---|---|---|
| *Saussurealappa* | Asteraceae | 200–400 | Cytoprotective effect | Sutar et al. [16] |
| *Zizyphusoenoplia* (L.) | Rhamnaceae | 300 | Increase in prostaglandin synthesis | Jadhav and Prasanna [17] |
| *Zizyphus lotus* (L.) | Lamiaceae | 50–200 | Cytoprotective agents | Wahida et al. [39] |
| *Quassiaamara* (L.) | Simaroubaceae | 4.9–48.9 | Increase in gastric barrier mucus and non-protein sulfhydril groups | Garcia-Barrantes and Badilla [29] |
| *Cocusnucifera* (L.) | Arecaceae | 100–200 | NA | Anosike and Obidoa [40] |
| *Encholiriumspectabile* | Bromeliaceae | 100 | Protection to gastric mucosa by activation of antioxidant systems and the involvement of prostaglandins and the NO synthase pathway | de Carvalho et al. [13] |
| *Cissusquadrangularis* (L.) | Vitaceae | 1000 | Protective effects | Shanthi et al. [41] |
| *Gynuraprocumbens (Merr.)* | Asteraceae | 400 | Protective effects | Mahmood et al. [42] |
| *ZingiberOfficinale Roscoe* | Zingiberaceae | 50–200 | Inhibition of ulcer index, prevented the oxidative damage of gastric mucosa by blocking lipid peroxidation, decrease in superoxide dismutase and increase in catalase activity | Arun et al. [15] |
| *Butea frondosa (Roxb.)* | Fabaceae | 250–500 | Gastroprotective activity | Londonkar and Ranirukmini, [18] |
| *Parkiaplatycephala* | Leguminosae | 62.5–250 | Gastroprotective activity, antioxidant effect through increase in catalase activity | Fernandes et al. [23] |
| *Anacardiumhumile* | Anacardiaceae | 50 | Protect gastric mucosa due to increased PGE2 and mucous production | Ferreira et al. [10] |
| *Rhizophora mangle* L. | Rhizophoraceae | 500 | Gastroprotective and antisecretory effects, in addition to increase in PGE2 levels | Sánchez et al. [32] |
| *Excoecariaagallocha* L. | Euphorbiaceae | 62.5–125 | Decreases the acidity and increases the mucosal defense in the gastric areas | Thirunavukkarasu et al. [11] |
| *Erythrinaindica* L. | Fabaceae | 125–500 | NA | Sachin and Archana [43] |
| *Glycyrrhizaglabra* L | Fabaceae | 200 | Mucosal protective and antioxidant effects on the gastric mucosa | Ligha and Fawehinmi [24] |
| *Virolasurinamensis (Rol. ex Rottb.) Kuntze* | Myristicaceae | 500 | Inhibited mucosal injury, reduced the formation of gastric lesions | Hiruma-Lima et al [44] |
| *Combretumleprosum Mart. &Eiche* | Combretaceae | | Inhibition of the gastric acid secretion and an increase of mucosal defensive factors | Nunes et al. [45] |
| *Gymnosporiarothiana (Walp.) Wight &Arn. ex M.A.Lawson* | Celastraceae | 250–500 | Increasing gastric mucosal defense (prostaglandin and free radical scavenging) | Jain and Surana [20] |
| *Spathodea falcate* | Bignoniaceae | 250–500 | Increasing gastric mucosal defense (prostaglandin and free radical scavenging) | Jain and Surana [46] |
| *Terminalia chebula Retz.* | Combretaceae | 250–500 | Inhibition of the gastric lesions due to its antisecretory | Raju et al. [26] |
| *Matricariachamomilla* L. | Asteraceae | 400 | NA | Karbalay-Doust and Noorafshan [30] |
| *Morus alba* L. *(mulberry)* | Moraaceae | 250–500 | Anti-inflammatory and antioxidant activity | Abdulla et al. [47] |
| *Camellia sinensis* | Theaceae | 10 | Healing of gastric ulcer restoration of cellular antioxidant status | Chatterjee et al. [48] |
| *Centaurea bruguier* | Asteraceae | 100 and 42 | Preventive activity against peptic ulcer | Khanavi et al. [49] |
| *Curcuma longa* L. | Zingiberaceae | 20 | Antiulcerogenic, antioxidant and antiinflammatory | Mahattanadul et al. [50] |

**Table 3**
List of some plants showing their part used as anti-ulcer activity.

| S.No. | Botanical Name | Common name | Family | Part Used |
|---|---|---|---|---|
| 1 | *Emblica officinalis* | Aamla | Euphorbiacae | Fruit &Dried bark extract |
| 2 | *Azadirachta indica* | Neem | Meliaceae | extract, Leaves |
| 3 | *Bacopa monniera* | Brahmi | Scrophulariaceae | Fresh Juice |
| 4 | *Carica papaya* | Papeeta | Caricaceae | Seeds |
| 5 | *Ocimum sanctum* | Tulsi | Labiatae | All plant parts |
| 6 | *Morinda citrifolia* | Mulberry | Rubiaceae | Fruit |
| 7 | *Allophylus serratus* | Tippani | Sapindaceae | Leaves |
| 8 | *Centella asiatica* | Gotu Kola | Apiaceae | Fresh Juice |
| 9 | *Desmodium gangeticum* | Shaparni | Leguminosae | Root Extract |
| 10 | *Asparagus racemosus* | Satavari | Liliaceae | Extract of fresh root |
| 11 | *Zingiber officinalis* | Ginger | Zingiberaceae | Powdered gingerrhizome |
| 12 | *Musa sapientum* | Banana, | Musaceae | Fruit |
| 13 | *Aloe vera* | Gritkumari | Liliaceae | Leaves |
| 14 | *Curcuma longa* | Haldi | Zingiberaceae | Rhizome |
| 15 | *Jatropha sativa* | Kalonji | Euphorbiaceae | Leaves |
| 16 | *Vitiveria ziziinoides* | Graminae | Benachar | Root |
| 17 | *Bauhinia racemosa* | Beedi leaf tree | Caesalpiniaceae | Flower buds |
| 18 | *Capsicum annuum* | Chilli | Solanaceae | Fruit |
| 19 | *Ageratum conyzoides* | Goat weed | Asteraceae | Leaves |
| 20 | *Trianthema pentandra* | Salsabuni | Aizoaceae | Whole plant |
| 21 | *Quercus ilex* | Oak | Fagaceae | Root bark |
| 22 | *Alstonia scholaris* | Saptaparn | Apocynaceae | Leaves |
| 23 | *Punica granatum* | Anaar | Lythraceae | Fruit peel |
| 24 | *Ficus religiosa* | Pipal | Moraceae | Leaves |
| 25 | *Momordica charantia* | Karela | Cucurbitaceae | Seeds |
| 26 | *Benincasa hipsida* | Pethakaddu | Cucurbitaceae | Fruits |

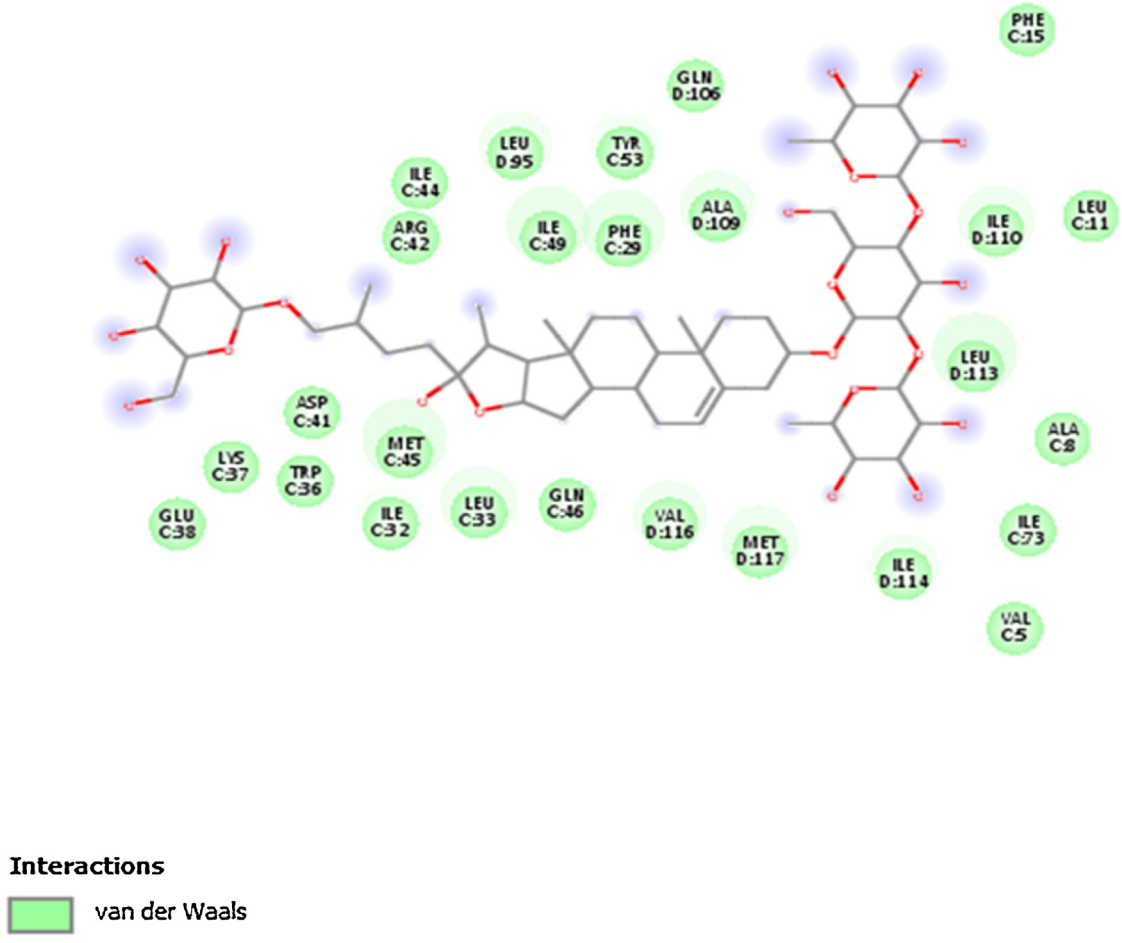


**Fig. 3.** Interaction of Protodioscin with anti-ulcer (Interferon-y).

*Magnolia sieboldii* [58], oil-macerated garlic constituents [59] and *Aristolochia paucinervis* [60].

Adesanwo et al. [61] studied the antiulcerogenic effect of *Melaleuca bracteata* stem bark extract and showed thatthe extract significantly reduced gastric acid secretion. They also reported that the bark extract contains two important constituents' betulinic acid and oleanolic acid, play major role in anti-ulcer effect. In another attempt, Agrawal et al. [62] studied the antiulcer activity of petroleum ether, alcohol and aqueous extracts of *Smithia conferta.* Phytochemical analysis of petroleum ether extract found to have steroids, alcohol extract constitute isoflavonoids, alkaloids and carbohydrates whereas in the aqueous extract significant amount of amino acids, carbohydrates and flavonoids were present. However, the aqueous and alcoholic extracts showed significant reduction in ulcer index compared to petroleum ether extract. All through in our evolution, natural products have enormous eminence in the fields of medicine and health. Natural products along being the earth friendly, they are free from any adverse effect to the human health.

## 5. Future prospective

Plant metabolites (natural products) have been the most successful source of potential drugs since ancient period [63]. However, due to the emergence of new human diseases with the changing environment, continuous screening and validation of secondary metabolites in the form of drug identification/designing needs to be updated. Different cheminformatics approaches like target identification, active site prediction, drug likeliness properties, biological activity and molecular docking of selected phytoligands are the key features for identifying for functional aspects of any drug.

Secondary metabolites of the plants have been recognized to elicit beneficial effects in virulent factors of diseases. The raw materials and pharmaceuticals needed for the preparation of essential drugs are largely obtained from the local herbal plants [64]. The revolution of metabolic engineering and the development molecular docking algorithms approaches lead to improved molecular simulations with crucial applications in virtual high-throughput screening and drug discovery. Analysis with molecular docking of interactions between protein-ligand, become an emerging tool in drug design [65].

In case of *Helicobacter pylori* infected individuals, the frequencies of virulent factor IFNγ cells have been increased in the antrum, which induces development of gastric ulcers [66]. Protodioscin a secondary metabolites of *Asparagus racemosus* is used as medicinal compounds against several diseases [67]. The analysis by molecular docking between the virulent factor and plant metabolites showed the interaction between structural protodioscin (PubChem CID: 441891) and interferon-γ (PDB ID: 1hig), in which all residues of interferon-γ exhibited hydrophobic interactions (Fig.3). Although, the obtained binding energy (−26.96 kcal/mol) of protodioscin- interferon-γ complex revealed disruptions of interferon-γ integrity. These types of interactions between the virulent factors of ulcer and plants secondary metabolites open a new door in the field of designing and discovery of a new drug in the ulcer treatment.

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## Conflict of interest

No any authors have conflict of interest.

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## References

[1] B.B. Petrovska, Historical review of medicinal plants' usage, Pharmacog. Rev. 6 (11) (2012) 1.
[2] W.A. Wannes, B. Marzouk, Research progress of Tunisian medicinal plants used for acute diabetes, J. Acute Dis. 5 (2016) 357–363.
[3] P. Prashantkumar, G.M. Vidyasagar, Traditional Knowledge on Medicinal Plants used for the Treatment of Skin Diseases in Bidar District Karnataka, (2013) .
[4] K. Anand, C. Tiloke, P. Naidoo, A.A. Chuturgoon, Phytonanotherapy for management of diabetes using green synthesis nanoparticles, J. Photochem. Photobiol. B: Biol. 173 (2017) 626–639.
[5] M.S. Zelickson, C.M. Bronder, B.L. Johnson, J.A. Camunas, D.E. Smith, D. Rawlinson, S. Von, H.H. Stone, S.M. Taylor, Helicobacter pylori is not the predominant etiology for peptic ulcers requiring operation, Am. Surg. 77 (2011) 1054–1060.
[6] K.T. Chung, V.G. Shelat, Perforated peptic ulcer-an update, World J. Gastrointest. Surg. 9 (2017) 1.
[7] D. Mehta, Ulcer-review on types, anti-ulcer drugs, anti-ulcer medicinal plants, anti-ulcer drug market, diagnostics and current global clinical trials status, Invent. Rapid Pharm. Pract. 2 (2016) 1–8.
[8] H. Kalant, D.M. Grant, Principle of Medical Pharmacology, 7th ed., Elsevier, 2007 ISBN-978-0-7796-9945-2.
[9] J.R. Malagelada, E.J. Kuipers, M.J. Blaser, Acid Peptic Disease: Clinical Manifestations Diagnosis Treatment and Prognosis, Cecil Medicine, 23rd ed., Saunders Elsevier, Philadelphia PA, 2007.
[10] A.L. Ferreira, A.C.A. Almeida, M. Cola, V. Barbastefano, A.B.A. Almeida, L.M. Batista, E.F. Silva, C.H. Pellizzon, C.A. Hiruma-Lima, L.C. Santos, W. Vilegas, A.R. M.S. Brito, Mechanisms of the gastric antiulcerogenic activity of *Anacardium humile* St. Hil on ethanol-induced acute gastric mucosal injury in rats, Molecules 15 (2010) 7153–7166.
[11] P. Thirunavukkarasu, L. Ramkumar, T. Ramanathan, Antiulcer activity of *Excoecaria agallocha* bark on NSAID-induced gastric ulcer in albino rats, Glob. J. Pharmacol. 3 (2009) 123–126.
[12] T.S. Muralidhar, A. Balaji, C. Bandopadhyay, S.L. Shantha, Cytoprotective effect of ulgen a polyherbal formulation against physical and chemical factor induced gastric ulcers in Wister albino rats, Am. J. Pharmacol. Toxicol. 4 (2009) 80–84.
[13] K.I. de Carvalho, H.B. Fernandes, F.D.F. Machado, I.S. Oliveira, F.A. Oliveira, P.H. M. Nunes, J.T. Lima, J.R.G.S. Almeida, R.C.M. Oliveira, Antiulcer activity of ethanolic extract of *Encholirium spectabile* Mart. ex Schult & Schult f. (Bromeliaceae) in rodents, Biol Res. 43 (2010) 459–465.
[14] E.S.S. Almeida, V.C. Filho, R. Niero, B.K. Clasen, S.O. Balogun, D.T.O. Martins, Pharmacological mechanisms underlying the anti-ulcer activity of methanol extract and canthin-6-one of *Simaba ferruginea* A. St-Hil in animal models, J. Ethnophar. 12 (2011) 630–636.
[15] K. Arun, Ch V. Rao, V.M. Kumar, A. Ayaza, S. Naiyera, K.M. Irfan, Anti-ulcerogenic and ulcer healing effects of *Zingiber officinale* (L.) on experimental ulcer models: possible mechanism for the inhibition of acid formation, Int. J. Pharm. Res. 1 (2010) 75–85.
[16] N. Sutar, R. Garai, U.S. Sharma, N. Singh, S.D. Roy, Antiulcerogenic activity of *Saussurea lappa* root, Int. J. Pharm. Life Sci. 2 (2011) 516–520.
[17] S.A. Jadhav, S.M. Prasanna, Evaluation of antiulcer activity of *Zizyphus oenoplia* (L) Mill. Root in rats, Asian J. Pharmaceut. Clin. Res. 4 (2011) 92–95.
[18] R.L. Londonkar, R.K. Ranirukmini, Antiulcerogenic study of different extracts of *Butea frondosa* Roxb in albino mice, J. Pharmacog. 1 (2010) 6–9.
[19] J.E. Okokon, B.S. Antia, E.E. Umoh, Antiulcerogenic activity of ethanolic leaf extract of *Lasianthera Africana*, Afr. J. Tradit. Compl. Altern. Med. 6 (2009) 150–154.
[20] A.S. Jain, S.J. Surana, Antiulcerogenic effects of *Gymnosporia rothiana* (Celastraceae) against different experimental models, Pharmacog. Mag. 5 (2009) 100–104.
[21] P.M. Mazumder, D. Sasmal, R.A. Nambi, Antiulcerogenic and antioxidant effects of *Coccinia granids* (Linn.) Voigt leaves on aspirin-induced gastric ulcer in rats, Nat. Prod. Rad. 7 (2008) 15–18.
[22] M. Minaiyan, A. Ghannadi, E. Salehi, Antiulcerogenic effect of *Zataria multiflora* boiss. On cysteamine induced duodenal ulcer in rats, Iran. J. Pharm. Sci. 1 (2005) 223–229.
[23] H.B. Fernandes, F.V. Silva, F.F.B. Passos, R.D.S. Bezerra, M.H. Chaves, F.A. Oliveira, R.C.M. Oliveira, Gastroprotective effect of the ethanolic extract of *Parkia platycephala* Benth. Leaves against acute gastric lesion models in rodents, Biol. Res. 43 (2010) 451–457.
[24] A.E. Ligha, H.B. Fawehinmi, Protection by liquorice in alcohol induced gastric mucosa damage, Pak. J. Nutr. 8 (2009) 1532–1536.
[25] A. Ologundudu, A.O. Lawal, I.A. Ololade, A.A. Omonkhua, F.O. Obi, The anti-ulcerogenic activity of aqueous extract of carica papaya fruit on aspirin—induced ulcer in rats, Int. J. Toxicol. 5 (2008) 2.

[26] D. Raju, K. Ilango, V. Chitra, K. Ashish, Evaluation of antiulcer activity of methanolic extract of *Terminalia chebula* fruits in experimental rats, J. Pharm. Sci. Res. 1 (2009) 101–107.
[27] A.E. Bighettia, M.A. Antonioa, L.K. Kohna, V.L.G. Rehdera, M.A. Foglioa, A. Possentia, L. Vilelaa, J.E. Carvalhoa, Antiulcerogenic activity of a crude hydroalcoholic extract and coumarin isolated from *Mikania laevigata* Schultz Bip, Phytomedicine 12 (2005) 72–77.
[28] P.A. Nwafor, T.W. Jacks, A.U. Ekanem, C.F. Poh, Antiulcerogenic and antidiarrhoeal potentials of methanolic extract of *Pausinystalia macroceras* stem-bark in rats, Nig. J. Nat. Prod. Med. 9 (2005) 63–67.
[29] P.M. Garcia-Barrantes, B. Badilla, Anti-ulcerogenic properties of *Quassia amara* L (Simaroubaceae) standardized extracts in rodent models, J. Ethnophar. 12 (2011) 904–910.
[30] S. Karbalay-Doust, A. Noorafshan, Antiulcerogenic effects of *Matricaria chamomilla* extract in experimental gastric ulcer in mice, Iran. J. Med. Sci. 34 (2009) 198–203.
[31] V. Molina, D. Carbajal, L. Arruzazabala, R. Más, Therapeutic effect of D-002 (Abexol) on gastric ulcer induced experimentally in rats, J. Med. Food 8 (2005) 59–62.
[32] L.M.P. Sańchez, A. Escobar, C. Souccar, M.A.R. Antonia, B. Mancebo, Pharmacological and toxicological evaluation of *Rhizophora mangle* L, as a potential antiulcerogenic drug: chemical composition of active extract, J. Pharmacog. Phytother. 2 (2010) 56–63.
[33] R.L. Londonkar, P.V. Poddar, Studies on activity of various extracts of *Mentha arvensis* Linn. against drug induced gastric ulcer in mammals, World J. Gastrointest. Oncol. 1 (2009) 82–88.
[34] P. Malairajan, G. Gopalakrishna, S. Narasimhan, K.J. Kala Veni, Evaluation of anti-ulcer activity of *Polyalthia longifolia* (Sonn) Thwaites in experimental animals, Ind. J. Pharmacol. 40 (2008) 126–128.
[35] E. Sanmugapriya, S. Venkataraman, Antiulcerogenic potential of *Strychnos potatorum* Linn seeds on aspirin plus pyloric ligation-induced ulcers in experimental rats, Int. J. Phytother. Phytopharmacol. 14 (2007) 360–366.
[36] A.S. Awaad, D.J. Maitland, G.A. Soliman, Antiulcerogenic activity of *Alhagi maurorum*, Pharm. Biol. 44 (2006) 292–296.
[37] M. Cola-Miranda, V. Barbastefano, C.A. Hiruma-Lima, T.R. Calvo, W. Vilegas, A. R.M.S. Brito, Antiulcerogenic activity of *Indigofera truxillensis* Kunth, Biota Neotropica 6 (2006) 0–0.
[38] R.G. Coelho, L.M. Batista, L.C. Santos, A.R.M.S. Brito, W. Vilegas, Phytochemical study and antiulcerogenic activity of *Syngonanthus bisulcatus* (Eriocaulaceae), Braz. J. Pharm. Sci. 42 (2006) 413–417.
[39] B. Wahida, B. Abderrahman, C. Nabil, Antiulcerogenic activity of *Zizyphus lotus* (L.) extracts, J. Ethnopharmacol. 112 (2007) 228–231.
[40] C.A. Anosike, O. Obidoa, Anti-inflammatory and antiulcerogenic effect of ethanol extract of coconut (*Cocos nucifera*) on experimental rats, Afr. J. Food Agri. Nutr. Dev. 10 (2010) 4286–4300.
[41] G. Shanthi, G. Vijay kanth, L. Hitesh, M. Ganesan, Antiulcerogenic activities of the methanolic extract of *Cissus quadrangularis* in wistar, Int. J. Toxicol. 7 (2010) 1559–3916.
[42] A.A. Mahmood, A.A. Mariod, F. Al-Bayaty, S.I. Abdel-Wahab, Anti-ulcerogenic activity of *Gynura procumbens* leaf extract against experimentally-induced gastric lesions in rats, J. Med. Plants Res. 4 (2010) 685–691.
[43] S.S. Sachin, J.R. Archana, Antiulcer activity of methanol extract of *Erythrina indica* lam. Leaves in experimental animals, Pharmacog. Res. 1 (2009) 396–401.
[44] C.A. Hiruma-Lima, L.M. Batista, A.B.A. Almeida, L.P. Magri, L.C. dos Santos, W. Vilega, A.R.M.S. Brito, Antiulcerogenic action of ethanolic extract of the resin from *Virola surinamensis* Warb. (Myristicaceae), J. Ethnophar. 122 (2009) 406–409.
[45] P.H.M. Nunes, P.M.S. Cavalcanti, S.M.P. Galvao, M.C.C. Martins, Antiulcerogenic activity of *Combretum leprosum*, Pharmazie 64 (2009) 58–62.
[46] A.S. Jain, S.J. Surana, Antiulcerogenic effects of *Spathodea falcata* against different experimental models, Asian J. Pharm. Clin. Res. 2 (2009) 54–59.
[47] M.A. Abdulla, H.M. Ali, K.A. Ahmed, S.M. Noor, S. Ismail, Evaluation of the anti-ulcer activities of *Morus alba* extracts in experimentally-induced gastric ulcer in rats, Biomed. Res. 20 (2009) 35–39.
[48] S. Chatterjee, A. Chatterjee, S. Roy, B. Bera, S.K. Bandyopadhyay, l-theanine healed NSAID-induced gastric ulcer by modulating pro/antioxidant balance in gastric ulcer margin, J. Nat. Med. 68 (2014) 699–708.
[49] M. Khanavi, R. Ahmadi, A. Rajabi, S.J. Arfaee, G. Hassanzadeh, R. Khademi, A. Hadjiakhoondi, C. Beyer, M. Sharifzadeh, Pharmacological and histological effects of Centaurea bruguierana ssp. belangerana on indomethacin-induced peptic ulcer in rats, J. Nat. Med. 66 (2012) 343–349.
[50] S. Mahattanadul, N. Radenahmad, N. Phadoongsombut, T. Chuchom, P. Panichayupakaranant, S. Yano, W. Reanmongkol, Effects of curcumin on reflux esophagitis in rats, J. Nat. Med. 60 (2006) 198–205.
[51] H. Xiao, P. Heeringa, P. Hu, Z. Liu, M. Zhao, Y. Aratani, N. Maeda, R.J. Falk, J.C. Jennette, Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice, J. Clin. Invest. 110 (2002) 955.
[52] A. Ohsaki, J. Takashima, N. Chiba, M. Kawamura, Microanalysis of a selective potent anti-*Helicobacter pylori* compound in a Brazilian medicinal plant *Myroxylon peruiferum* and the activity of analogues, Bioorg. Med. Chem. Lett. 9 (1999) 1109–1112.
[53] T. Fukai, A. Marumo, K. Kaitou, T. Kanda, S. Terada, T. Nomura, Anti-*Helicobacter pylori* flavonoids from *Licorice* extract, Life Sci. 71 (2002) 1449–1463.
[54] Y. Li, C. Xu, Q. Zhang, J.Y. Liu, R.X. Tan, In vitro anti-*Helicobacter pylori* action of 30 Chinese herbal medicines used to treat ulcer diseases, J. Ethnophar. 98 (2005) 329–333.
[55] J.C. Yang, T.H. Wang, H.J. Wang, C.H. Kuo, J.T. Wang, W.C. Wang, Genetic analysis of the cytotoxin-associated gene and the vacuolating toxin gene in *Helicobacter pylori* strains isolated from Taiwanese patients, Am. J. Gastroenterol. 92 (8) (1997).
[56] H. Matsuda, I. Toguchida, K. Ninomiya, T. Kageura, T. Morikawa, M. Yoshikawa, Effects of sesquiterpenes and amino acid-sesquiterpene conjugates from the roots of *Saussurea lappa* on inducible nitric oxide synthase and heat shock protein in lipopolysaccharide-activated macrophages, Bioorg. Med. Chem. 11 (2003) 709–715.
[57] M.M. Cowan, Plant products as antimicrobial agents, Clin. Microbiol. Rev. 12 (1999) 564–582.
[58] B.J. Park, C.K. Lee, H.J. Park, Anti-*Helicobacter pylori* effect of costunolide isolated from the stem bark of *Magnolia sieboldii*, Arch. Pharm. Res. 20 (1997) 275–279.
[59] R. Ohta, N. Yamada, H. Kaneko, K. Ishikawa, H. Fukuda, T. Fujino, A. Suzuki, In vitro inhibition of the growth of *Helicobacter pylori* by oil-macerated garlic constituents, Antimicrob. Agents Chemother. 43 (1999) 1811–1812.
[60] C.A. Gadhi, F. Mory, A. Benharref, C. Lion, M. Jana, M. Weber, A. Lozniewski, Antibacterial activity of *Aristolochia paucinervis* Pomel, J. Ethnophar. 67 (1999) 87–92.
[61] J.K. Adesanwo, F.O. Shode, O.O. Aiyelaagbe, O.O. Rabiu, R.T. Oyede, F.S. Oluwole, Antisecretory and antiulcerogenic activities of the stem bark extract of *Melaleuca bracteata* and isolation of principles, J. Med. Plants Res. 3 (2009) 822–824.
[62] R. Agrawal, H.K. Garg, U. Garg, S.K. Singh, Anti-ulcer activity of *Smithia conferta* in various animal, J. Saudi Chem. Soc. 14 (2010) 307–310.
[63] D.A. Dias, S. Urban, U. Roessner, A historical overview of natural products in drug discovery, Metabolites 2 (2012) 303–336.
[64] A. Ota, N.P. Ulrih, An overview of herbal products and secondary metabolites used for management of type two diabetes, Front. Pharmacol. 8 (2017).
[65] S. Vilar, E. Sobarzo-Sánchez, L. Santana, E. Uriarte, Molecular docking and drug discovery in β-adrenergic receptors, Curr. Med. Chem. 24 (39) (2017) 4340–4359.
[66] J. Adamsson, L.S. Ottsjö, S.B. Lundin, A.M. Svennerholm, S. Raghavan, Gastric expression of IL-17A and IFNγ in *Helicobacter pylori* infected individuals is related to symptoms, Cytok 99 (2017) 30–34.
[67] Y. Jaiswal, Z. Liang, A. Ho, H. Chen, Z. Zhao, A comparative tissue-specific metabolite analysis and determination of protodioscin content in Asparagus species used in traditional Chinese medicine and ayurveda by use of laser microdissection UHPLC–QTOF/MS and LC–MS/MS, Phytochem. Anal. 25 (2014) 514–528.