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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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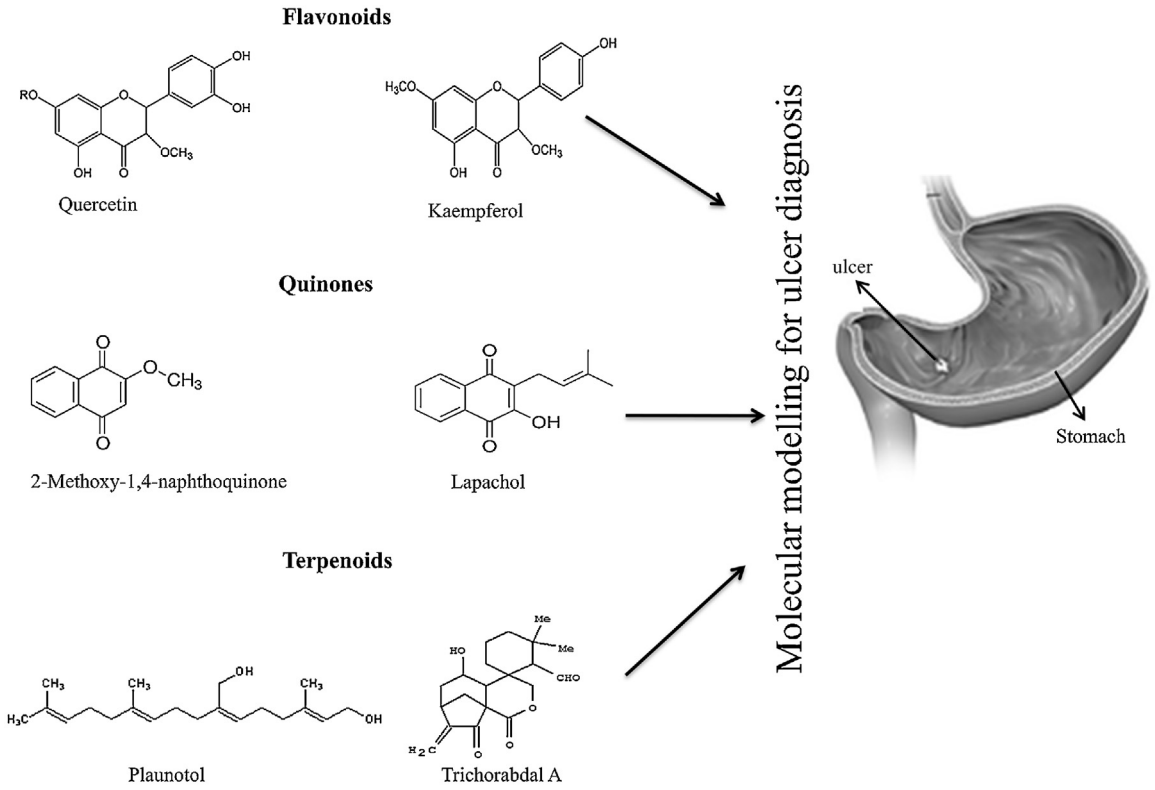

Fig. 1. Overview of anti-ulcer metabolites from plant.

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

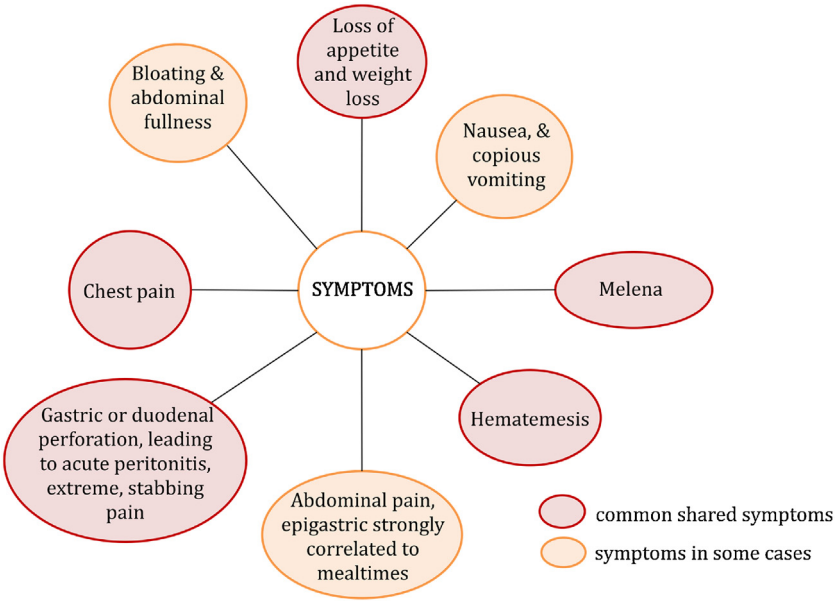

Fig. 2. Some common symptoms of ulcer.

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

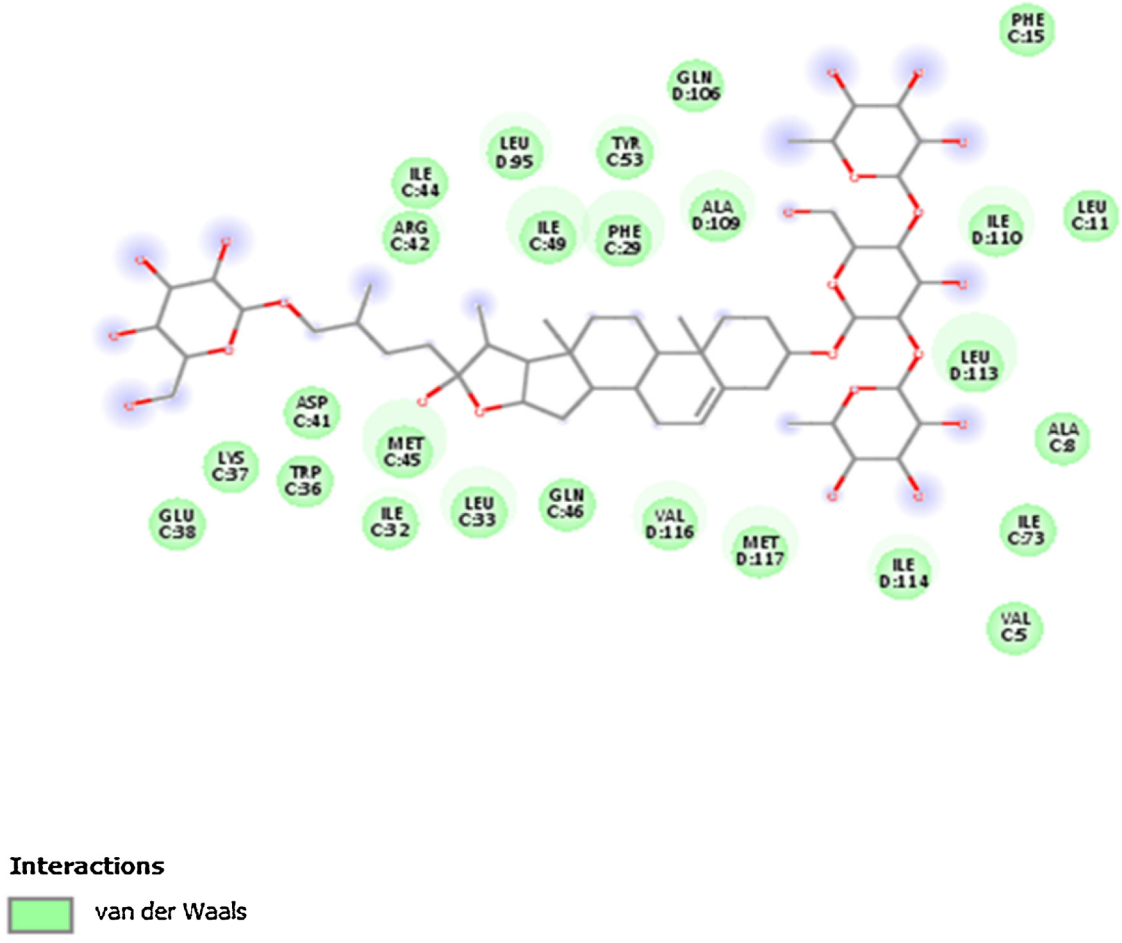

Fig. 3. Interaction of Protodioscin with anti-ulcer (Interferon-y).

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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