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Medicinal Plants with Antibacterial Properties Against *Helicobacter pylori*: A Brief Review

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Abstract

Helicobacter pylori (H. pylori) is one of the most common worldwide human infections. It is estimated over half of the Earth's population are infected with this bacterium. This pathogen is a causative agent for many gastro-duodenal diseases, peptic ulcers and gastric cancer. In recent years, emerging resistant to antibiotics limits their use in the treatment of this infection. As a result, many natural products have been studied to find new effective alternative drugs against difficult to treat *H. pylori* giving special attention to plants used traditionally for a long time against gastrointestinal disorders. This review presents the potential of many medicinal plants to serve as promising sources for new and alternative anti-*H. pylori* agents.

Keywords: Medicinal plants; Anti-bacterial; Anti-*H. pylori*; *Helicobacter pylori*

Introduction

According to the World Health Organization (WHO), upto 80% of the world's population relies on the traditional medicine (Mostly from medicinal plants) for their primary health care needs [1]. Meaning that, only 20% of the world's population depends on Modern medicine (Mostly synthesized or semi-synthesized compounds). Moreover, up to 25% of the modern drugs are from plant origin, 11% of the essential and basic drugs are produced from plants and 60% of anti-tumor and anti-infectious drugs are initially from natural products [2]. The use of medicinal plants to heal diseases which is known as phytotherapy is as old as the human being. Medicinal plants have acquired their therapeutic properties from its ability to reproduce numerous and renewable secondary metabolites known as phytochemical compounds, Plants used these phytochemicals as a defense mechanism against macro-organisms as well as micro-organisms [3]. Recently, due to the constant emergence of resistant pathogens, almost all conventional antibiotics has been motivated the pharmaceutical companies to change their strategy and develop new antimicrobial drugs from medicinal plants [4]. Although, the synthetic antibiotics are the dominant antimicrobial drugs. Within the last three decades, incidences of infectious diseases has increased dramatically, including old infections with properties as well as new infections and it is reported that about 30 new infectious agents has been recorded, 60% of them are zoonotic origin (spread between animals and human), among them are *Helicobacter pylori* which may cause Duodenal, gastric ulcer and stomach cancer [5]. This review aimed to highlight some medicinal plants that recorded potential antibacterial activity against *Helicobacter pylori* that may be a candidate for use as a source of future effective drugs against this pathogen.

Helicobacter pylori infection

The human being has granted a complex normal flora ecosystem in many niches in the body, one of these niches is the gastrointestinal tract. The normal gastrointestinal microflora are stable in the normal individual and is essential for maintaining the eco-physiological balance in the gastrointestinal tract, and it was observed that there is an inverse relationship between the commensal microflora and the growth of *H. pylori* [6]. Marshall and Warren were the first who isolated *H. pylori* in 1983 from the gastric epithelium and proved that this bacterium is the cause of the most gastro-duodenal diseases, peptic ulcers and gastric cancer [7]. *H. pylori* is one of the most genetically diverse bacterium, (Helicobacter: a spiral rod, *pylori*: gate keeper), it is a small, spiral (S-shaped) or curved gram-negative motile bacilli, micro-aerophilic, non-sporing and coccal transformation occurs when exposed to air for about two hours [8,9]. About 50% of the world inhabitants are infected with *H. pylori*, this percentage may reach 80% in some developing countries and 40% in the developed industrial countries, and this explains why scientists believe that the prevalence of *H. pylori* could be inversely correlated with the socioeconomic situation and hygiene [10]. Ironically, in the developed industrialized countries there is a relatively high prevalence of gastric cancer, while the developing countries have low incidences of gastric cancer [8]. The mechanism of acquisition and transmission of *H. pylori* are still unknown. However, it is believed that the primary means of transmission are fecal-oral and gastro-oral route from person to person, contaminated food or water or via some domestic animals [10].

Treatment of *Helicobacter pylori*

In recent years, resistance to antibiotic therapy has dramatically increased while the ability to develop new antibiotics has decreased and the supply of new effective antibiotics expected to diminish in the future [3]. *H. pylori*, like other bacterial pathogens, has readily developed resistance to the antibiotics. Besides, it is difficult to treat pathogen, since the Sensitivity pattern of *H. pylori* to antibiotics *in vitro* differs from that *in vivo* due to the effects of the conditions into mucous epithelium cells of the stomach [9]. *H. pylori* characterized by a very high frequency of mutation (10-5-10-8) which are much larger than any other bacteria [11]. Since the discovery of *H. pylori* and consider it as a serious etiological agent of chronic gastritis and peptic ulcer, antibiotics such as amoxicillin, clarithromycin and tinidazole considered effective drugs [9]. Recently, as this pathogen is able to withstand to the single antibiotic therapy, a new strategy was invented to eradicate this infection. Accordingly, the triple therapy was invented, which is based on a combination of antibiotics, Bismuth sub-citrate and proton pump inhibitors, but this therapy is efficient for only 80% of patients and sometimes there is a possibility that the risk of infection returns after completion of the treatment [12]. Accordingly, the effectiveness of the commonly used therapies has been increasingly compromised by the rapid emerging of new resistant strains of *H. pylori*. Herein, medicinal plants could be a good alternative source of new anti-*H. pylori* drugs, or it could be used in synergy to alter the mode of action of the antibiotics and re-strengthened the common antibiotics that used against *H. pylori*.

Medicinal plants and *Helicobacter pylori*

There is a growing need to find new medications to be used against *H. pylori*, due to the widespread of this bacterium, its serious pathogenicity and emerging of many resistant strains. In literature, many plants and herbs revealed significant antibacterial activity against *H. pylori a*s shown in **(Table 1).**

Table 1: Medicinal plants having anti-*Helicobacter pylori* activity (*MIC: Minimum Inhibitory Concentration Test, **CD: Cup-Plate Diffusion Test, ***DD: Disk Diffusion Test, ****MBC: Minimum Bactericidal Concentration Test).

Plant name	Family	Part used	Extract	Method used	Activity	Reference
Achillea millefolium L.	Asteraceae	Aerial parts	Methanol	MIC*	50 µg/mL	Mahady et al. (2005)
Agrimonia pilosa Ledeb.	Rosaceae	indefinite	Aqueous	MIC	1:256 µg/ml	Li et al. (2013)
Allium sativum L.	Amaryllidaceae	Fresh cloves of the garlic pulp	Aqueous extract	MIC MBC	2-5 mg/ml 2-5 mg/ml	Cellini et al. (1996)
Alpinia speciosa K. Schum.	Zingiberaceae	Root	Ethanol extract	CD** MIC	11-20mm 5.12->5.12mg/ml	Wang and Huang (2005)
Anisomeles indica (L.) Kuntze	Lamiaceae	Leaves and stem	Ethanol extract	CD MIC	8-20mm 2.56-5.12mg/ml	Wang and Huang (2005)
Annona cherimola Mill.	Annonaceae	Leaves/stem	Methanol extract	MIC	<15.6 µg/ml	Castillo-Ju árez et al. (2009)
Artemisia ludoviciana subsp.*mexicana* (Willd. Ex Spreng) Fernald	Asteraceae	Leaves/stem	Aqueous extract	MIC	125 µg/ml	Castillo-Ju árez et al. (2009)
Bixa orellana L.	Bixaceae	seeds	96% ethanol	DD***	7-10 mm	Cogo et al. (2010)
Bombax malabaricum DC.	Malvaceae	Root	Ethanol extract	CD MIC	11-20 mm 1.28-5.12mg/ml	Wang and Huang (2005)
Byrsonima crassa Nied.	Malpighiaceae	Leaves	Methaanol and chloroform extract	MIC	1024 µg/ml	Bonacorsi et al. (2009)
Carum carvi L.	Apiaceae	Fruit	Methanol, di-ethyl ether and petroleum benzene	DD MIC	16-39 mm 31.25-125 µg/ml	Nariman et al. (2009)
Chamomilla recutita L.	Asteraceae	Inflorescence	96% ethanol	DD	10-11 mm	Cogo et al. (2010)
Cistus laurifolius L.	Cistaceae	Flowers	Chloroform fraction	MIC	1.95 µg/ml	Yesilada et al. (1999)
Coptis chinensis **Franch.**	Ranunculaceae	Rhizome	Aqueous	MIC	<1:512 µg/ml	Li et al. (2013)

Cuphea aequipetala Cav.	Lythraceae	Aerial parts	Aqueous extract	MIC	125 µg/ml	Castillo-Ju árez et al. (2009)
Curcuma amada Roxb.	Zingiberaceae	Rhizome	70% ethanol	MBC****	31.2-62.5 µg/ml	Zaidi et al. (2009)
Eugenia caryophyllata Thumb.	Myrtaceae	Flowers	Aqueous	MIC	1: 256 µg/ml	Li et al. (2013)
Foeniculum vulgare Mill.	Apiaceae(Umbelliferae)	Seeds	Methanol	MIC	50 µg/mL	Mahady et al. (2005)
Guaiacum coulteri A.Gray	Zygophyllaceae	Bark	Methanol extract	MIC	≤15.6 µg/ml	Castillo-Ju árez et al. (2009)
Houttuynia cordata Thunb.	Saururaceae	indefinite	Aqueous	MIC	1:512	Li et al. (2013)
Ilex paraguariensis A. *St.-Hil.*	Aquifoliaceae	Leaves	96% ethanol	DD	9-10 mm	Cogo et al. (2010)
Ludwigia repens J.R.Forst.	Onagraceae	Aerial parts	Aqueous extract	MIC	125 µg/ml	Castillo-Ju árez et al. (2009)
Mallotus phillipinesis (Lam) Muell.	Euphorbiaceae	Powder covering fruits	70% ethanol	MBC	15.6-31.2 µg/ml	Zaidi et al. (2009)
Malva sylvestris L.	Malvaceae	inflorescence and leaves	96% ethanol	DD	8-10 mm	Cogo et al. (2010)
Mentha piperita L.	Lamiaceae	Leaves/stem	Aqueous extract	MIC	<250 µg/ml	Castillo-Ju árez et al. (2009)
Moussonia deppeana (Schltdl. & Cham.) Klotzsch ex Hanst.	Gesneriaceae	Leaves/stem	Methanol extract	MIC	15.6 µg/ml	Castillo-Ju árez et al. (2009)
Myrisctica fragrans Houtt.	Myristacaceae	Seeds/aerial parts Seeds	70% ethanol Methanol	MBC MIC	31.2-125 µg/ml 12.5 µg/mL	Zaidi et al. (2009) Mahady et al. (2005)
Origanum majorana L.	Lamiaceae	Aerial parts	Methanol	MIC	50 µg/mL	Mahady et al. (2005)
Paederia scandens (Lour.) Merr.	Rubiaceae	Whole plant	Ethanol extract	CD MIC	11-16mm 0.64-5.12mg/ml	Wang and Huang (2005)
Passiflora incarnata L.	Passifloraceae	Aerial parts	Methanol	MIC	50 µg/mL	Mahady et al. (2005)
Persea Americana Mill.	Lauraceae	Leaves	Methanol extract	MIC	≤7.5 µg/ml	Castillo-Ju árez et al. (2009)
Plumbago zeylanica L.	Plumbaginaceae	Stem	Ethanol extract	CD MIC	11-20 mm 0.64-10.24mg/ml	Wang and Huang (2005)
Psoralea corylifolia L.	Papilionaceae	Seeds	70% ethanol	MBC	31.2-62.5 µg/ml	Zaidi et al. (2009)
Pteleopsis suberosa Engl. et Diels	Combretaceae	Bark	Methanol extract	MIC	31.25-250 µg/ml	Germanò et al. (1998)
Punica granatum L.	Punicaceae	Peel of fruit	methanol extracts	DD	27.96±0.97 mm	Moghaddam (2011)
Rhus chinensis Mill.	Anacardiaceae	Sumac	Aqueous	MIC	<1:512 µg/ml	Li et al. (2013)
Rosmarinus officinalis L.	Lamiaceae	Leaves	Methanol	MIC	25 µg/mL	Mahady et al (2005)
Terminalia spinosa Engl.	Combretaceae	Young branches	Crude extract	MIC	62.5-500 µg/ml	Fabry et al. (1996)
Trachyspermum copticum L.	Apiaceae	Fruit	Methanol, di-ethyl ether and petroleum benzene	DD MIC	25-43 mm 31.25-125 µg/ml	Nariman et al. (2009)
Xanthium brasilicum L.	Asteraceae	Aerial parts	Methanol, di-ethyl ether and petroleum benzene	DD MIC	25-34 mm 62.5-250 µg/ml	Nariman et al. (2009)
Zingiber officinale Roscoe	Zingiberaceae	Rhizome	Methanol	MIC	25 µg/mL	Mahady et al. (2005)

There are numerous plants showed anti-*H. pylori* activity, in this brief review, up to 41 plant species are reported to have potential anti-*H. pylori* activity, although these are not all plants studied worldwide and a comprehensive study is

required to cover all plants screened against *H. pylori*. Based on the literature gathered in this review, it was reported that, among 7 different plant species used in Brazilian traditional medicine against gastrointestinal disorders, 4 of them (*Bixa orellana, Chamomilla recutita, Ilex paraguariensis* and *Malva sylvestris*) showed different degrees of anti-*H. pylori* activity [13]. Up to 53 plants used in Mexican traditional medicine for gastrointestinal disorders were screened for their antibacterial effects against *H. pylori*, 7 of them have shown significant activity, namely, *Artemisia ludoviciana subsp. mexicana, Cuphea aequipetala, Ludwigia repens, Mentha piperita, Persea americana, Annona cherimola, Guaiacum coulteri, and Moussonia deppeana* [14]. Another study on 50 commonly used traditional medicinal plants from Pakistan were evaluated for their bactericidal effect against *H. pylori*, the most potent bactericidal activity was exhibited by 4 plant species, which were *Curcuma amada, Mallotus phillipinesis, Myrisctica fragrans and Psoralea corylifolia* [15]. 20 Iranian plant species were tested for their efficacy against *H. pylori* clinical isolates, 10 of them showed varied degrees of anti-*H. pylori* activity, but the highest activity showed with *Carum carvi, Xanthium brasilicum* and *Trachyspermum copticum* [16]. 40 Chinese herbs prescribed in the traditional medicine were studied for their anti-*H. pylori* activity, 5 of them possess higher potent activity, namely *Agrimonia pilosa, Coptis chinensis, Eugenia caryophyllata Houttuynia cordata and Rhus chinensis* [17]. 50 Taiwanese medicinal plants were examined for anti-*H. pylori* activity, five of them demonstrated strong activity which were; *Paederia scandens, Plumbago zeylanica, Anisomeles indica, Bombax malabaricum and Alpinia speciosa* [18]. In the USA, 24 plant species brought from different countries including the USA were screened *in vitro* against 15 strains of *H. pylori*, 7 plants considered as the most active anti-*H. pylori*, which were; *Myristica fragrans, Zingiber officinale, Rosmarinus officinalis, Achillea millefolium, Foeniculum vulgare, Passiflora incarnate* and *Origanum majorana* [19]. Moreover, many traditional plants from different regions were screened for anti-*H. pylori* activity and some of them showed potential effect, such as; Terminalia spinosa from east Africa [20], *Pteleopsis suberosa* from Mali [21], Byrsonima crassa from Brazil [22], *Punica granatum* From Iran [12], *Cistus laurifolius from* turkey [23] and garlic extract *(Allium sativum*) [24]. Since most of these screened plants have a long history of traditional uses against gastrointestinal disorders and some of them revealed anti-*H. pylori* comparable to antibiotics that are currently losing their efficacy against *H. pylori* due to emerging of resistant strains; Hence, the isolation of different potent compounds from the most active plant extracts is encouraging. Also, as shown in **(Table 1),** the *in vitro* studies for anti-*H. pylori* activity of medicinal plants are still lacking the standardization that would allow for the meaningful comparison and understanding the activity. Some studies used cup-plat or disc diffusion tests, others employed MIC or MBC or both. The data collected from these methods should allow other researchers to compare these results. Besides, the above-mentioned methods are known as basic methods (disc diffusion and agar or broth dilution), further deep antimicrobial studies must be implemented to support these findings such as time-kill method and flow cytofluorometric method which provides important information about the nature of the antibacterial compounds and their interactions in the prokaryotic cells [25].

Conclusion

As reviewed in this paper, it is obviously, there are numerous traditional plants potentially valuable sources of novel anti-*H. pylori* agents. However, most reports are on crud extracts, which gives general evaluation on the potency of these plants as anti-*H. pylori* agents but do not provide enough data on the complexity of these natural products to serve as drugs as well as the *in vivo* clinical studies. Accordingly, plants mentioned in this review could become the starting material for more integrated bioassay studies, such as fractionation to determine the active ingredients, understanding the mode of action of these plant extracts or compounds, low toxicity, cumulative effects and possible side effects as well as other significant pharmacological actions which could be beneficial for future drug development against *Helicobacter pylori.*

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