European Journal of Medicinal Plants
6(1): 1-16, 2015, Article no.EJMP.2015.037
ISSN: 2231-0894

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Evaluation of Multiple Functions of *Polygonum* Genus Compounds

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AHLN, LM, HKW, PT and OLF designed and wrote the review. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/EJMP/2015/15134
Editor(s):
(1) Marcello Iriti, Faculty of Plant Biology and Pathology, Department of Agricultural and Environmental Sciences, Milan State University, Italy.
Reviewers:
(1) Gyula Oros, PPI HAS, Budapest, Hungary.
(2) Isiaka A. Ogunwande, Natural Product Research Unit, Department of Chemistry, Faculty of Science, Lagos State University, Ojo, Nigeria.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=793&id=13&aid=7467

Review Article

Received 8th November 2014
Accepted 25th November 2014
Published 26th December 2014

ABSTRACT

For thousands of years, traditional medicinal plants have been used to control several diseases, based on traditional knowledge and experience. Nevertheless, many potential medicinal plants have not attracted attention to their useful pharmacological properties and remain to be discovered. In recent years, a number of plants from various genera, species and families have been scientifically studied for their pharmacological potential. Among them, the genus *Polygonum* contains 300 species worldwide. Many document reported various studies of phytochemical and pharmacological potential of crude extracts and compounds isolated from several *Polygonum* species.

Aims: The present review describes some traditional uses from the *Polygonum* genus, the phytochemistry, the pharmacological effects, the pharmacokinetics, the toxicology and the known potential phytoconstituents of therapeutic importance that have been isolated.

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Dschang, Dschang, Cameroon and Centro de Analises Proteômicas e Bioquimicas, Pós-Graduação em Ciencias Genomicas e Biotecnologia, Universidade Catolica de Brasilia, Brasilia, DF, Brazil, between September 2012 and September 2013.

Methodology: A review of literature was carried out using several resources such as scientific papers, classical books, pubmed, Scifinder, Sirus, the web of Science and ethnobotanical information.

Results: Plants from *Polygonum* are widely distributed in the world and used as traditional medicine. Several compounds including phenolic compounds (flavonoids, chalcones, stibenes, coumarins and others) have been isolated and characterized from these plants and some of them are used as the effective pre-clinical to control various diseases in the world.

Conclusion: The present review covers many medicinal properties of some species from the *Polygonum* genus, setting out further mechanism of actions and toxicity yet to be established. Studies on *Polygonum* plant extracts could be targeted to develop novel anticancer, anti allergic agents, potential antiplasmodial and anti-inflammatory drugs, from the active compounds. Apart from this, a new approach could be developed for preparing this herbal product, as well as in combination with other plants. Other pharmacological properties for use in artherosclerosis, neurological disorders, diabetes, hypertension and immunomodulatory effects should be evaluated.

Keywords: Polygonum; Polygonaceae; metabolites; phytoconstituents; pharmacological potential.

1. INTRODUCTION

Traditional medicinal plants have long been used in the cure of several human and animal diseases, based on knowledge and experience. Many of these plants have not been studied scientifically and therefore their active principles are still undiscovered. Even though herbal plants in crude form are available for treatment in folk medicine, their uses and activities have unproven track records. In recent years, a number of medicinal plants from various genera, species and families have been scientifically evaluated. Many active principles have been isolated and evaluated for their role in the prevention, control and treatment of many disease conditions.

The *Polygonum* genus contains 300 species found all over the world. They contain diverse pharmacologically active constituents with various properties [1]. These species are predominantly herbs, found in tropical and temperate regions [2]. Some species are important traditional medicines, as illustrated in Fig. 1. Many of these *Polygonum* species and their active principles have been studied for phytochemical screening, biological and pharmacological purposes. Some of them have shown efficacy in the prevention and treatment of diseases such as cancer, malaria, gastric ulcers, bacterial and fungal infections; their toxic effects have also been evaluated.

The present review focuses on some traditional plants from the *Polygonum* genus, their pharmacological and biological effects, and the known phytochemicals of potential therapeutic importance that have been isolated.

2. BOTANY

Polygonaceae family contains several genus includes *Polygonum* which is one of most important. *Polygonum* name is from the Greek poly, "many" and gonu, "knee" referring to the swollen-jointed stem. Different species from *Polygonum* genus vary widely from prostrate herbaceous annual plants (4-5 cm high) to herbaceous perennial plants (3–4 m tall). Others are trees or perennial woody vines and grow to around 20–30 m high, or trees. Many species are aquatic and naturally grow in the swampy area as floating plants in the rivers or ponds. The leaves vary in shape between from lanceolate to oval forms. They range from 1 to 30 cm long. The stems are usually red, reddish and sometime red-speckled. Generally, flowers are formed in dense clusters from the leaf joints and the youngest are white, pink or greenish [2].

3. TRADITIONAL USES

In China, “Rèlínqīng Kēlì” is the name of *Polygonum* extract. It’s used in the folk medicine to cure urinary tract infections [3]. According to the Chinese Pharmacopoeia, *P. cuspidatum* has been used to relieve joint pain, to treat jaundice caused by a bacterial infection or fungal problems and cough with amenorrheal expectoration. *Polygonum cuspidatum* is also called “Hu Zhang” in China, and is used as a

decoction to treat liver diseases or as a cream for topical application in burns, wounds and traumatic injuries [4]. It's currently also used in different forms such as powder, decoction or infusion to cure hepatitis and several other diseases [5]. In Korea, the rhizomes of *P. cuspidatum* are commonly used to maintain oral and dental hygiene [6]. In traditional Chinese medicine, *Polygonum multiflorum* has been used to treat mental and physical signs of aging, malaria, constipation and eczema. In Cameroonian traditional medicine, the raffia wine and aqueous extracts of the leaves of *Polygonum limbatum* are respectively used to cure gastrointestinal disorders, venereal diseases and skin infections [7]. In India, preparations of *Polygonum nepalense* are employed in colds, influenza, swelling, hemorrhoids, diarrhea and rheumatism [8]. The juice extract of the whole plant is taken orally for fetal mal-position and the decoction is also taken orally for juvenile pregnancy in Cameroon [9]. In Argentina, *Polygonum ferrurgineum* is used to heal infected wounds in local medicine¸ it's also used to control several bacteria and fungi [10]. In Bangladesh *Polygonum lapathifolium* is used as an insecticide [11]. In Brazil, *Polygonum spectabile* is used by indigenous people for the treatment of diarrhea, ulcers, gingivitis, skin infections and rheumatism [12]. *Polygonum hydropiper* is used as spice to flavor foods by Chinese and Malaysian indigenous because this specie possesses strong peppery taste [13]. In Turkey, the roots of *Polygonum amphibium* are very important in folk medicine and are used as an astringent and cleanser for skin [14,15]; they are also eaten raw, or sometimes they are dried, pounded and the infusion is used in the treatment of chest colds [16]. These data show that the *Polygonum* genus is widely distributed around the world and is being used on all continents to control numerous illnesses.

4. PHYTOCHEMISTRY

Several investigations were carried out to determine the possible chemical components from *Polygonum* plants. This genus is also well known for producing a wide variety of secondary metabolites including flavonoids [13], triterpenoids [17], anthraquinones [18], coumarins [19], phenylpropanoids [20], lignans [21], sesquiterpenoids [22], stilbenoids [23], tannins [1], proteins, amino acids and carbohydrates [8], and sucrose phenyl propanoid esters [19]. Amongst them, flavonoids are the most common components found in *Polygonum* spp. and have been used as chemotaxonomic markers of the genus [22]. Fig. 1. presents some bioactive compounds obtained from the *Polygonum* genus and Table 1. shows the pharmacological effects of some extracts and compounds isolated from some *Polygonum* plants. In summary, the present review focuses on studies of a number of traditional medicinal plants from the *Polygonum* genus, their pharmacological and biological effects, and the known potential phytoconstituents of therapeutic importance isolated so far.

5. PHARMACOLOGICAL EFFECTS

5.1 Anticancer Effects

Recently, Hu and coworkers studied the activities of aqueous *Polygonum cuspidatum* extract on hepatocarcinoma cells (Bel-7402 and Hepa 1-6) in suspension [4]. In this study, the sample (extract) significantly ($P<0.05$) inhibited the proliferation of these cells in suspension in a dose-dependent and time-dependent manner. This extract also respectively showed the significant inhibition and induction of hepatocarcinoma cells in soft agar and anoikis in human Bel -7402 cells. Previously, crude extracts and compounds such as emodin and resveratrol showed anticancer activities [24,25]. The growth of cancer cells specially Ehrlich's carcinoma was inhibited by aqueous extracts (20 g/kg/day) [25], alternatively the ethanol extract showed an antiproliferative activity against two different cancer cells (human Lung H1650 and A549), in a dose-dependent manner [26]. Resveratrol reduced by using 2.5 and 10 $mg.kg^{-1}$ for 5 days the volume and the weight of Lewis Lung tumor respectively (42%) and (44%). The tumor growth and metastasis in lungs are prevented by resveratrol (56%) [27]. Using resveratrol, several significant anticancer activities have been obtained by different research team. In an experiment on rats with intracerebral gliomas, the molecule (40 mg/kg/day, 150 days) exhibited anticancer activity such as higher and longer rat survival time and slower tumor growth [24]. Resveratrol in other experiments also showed cytotoxicity activities against lymph cancer [28], hepatic cancer [29], MCF-7 cells with IC50 (58.4 $\mu g.mL^{-1}$) and adriamycin-resistant MCF-7 cells with IC50 (56.7 $\mu g.mL^{-1}$) [30], ovarian cancer [31], human neuroblastomas and uveal melanoma tumors [32], atypical teratoid or rhabdoid tumors [33].

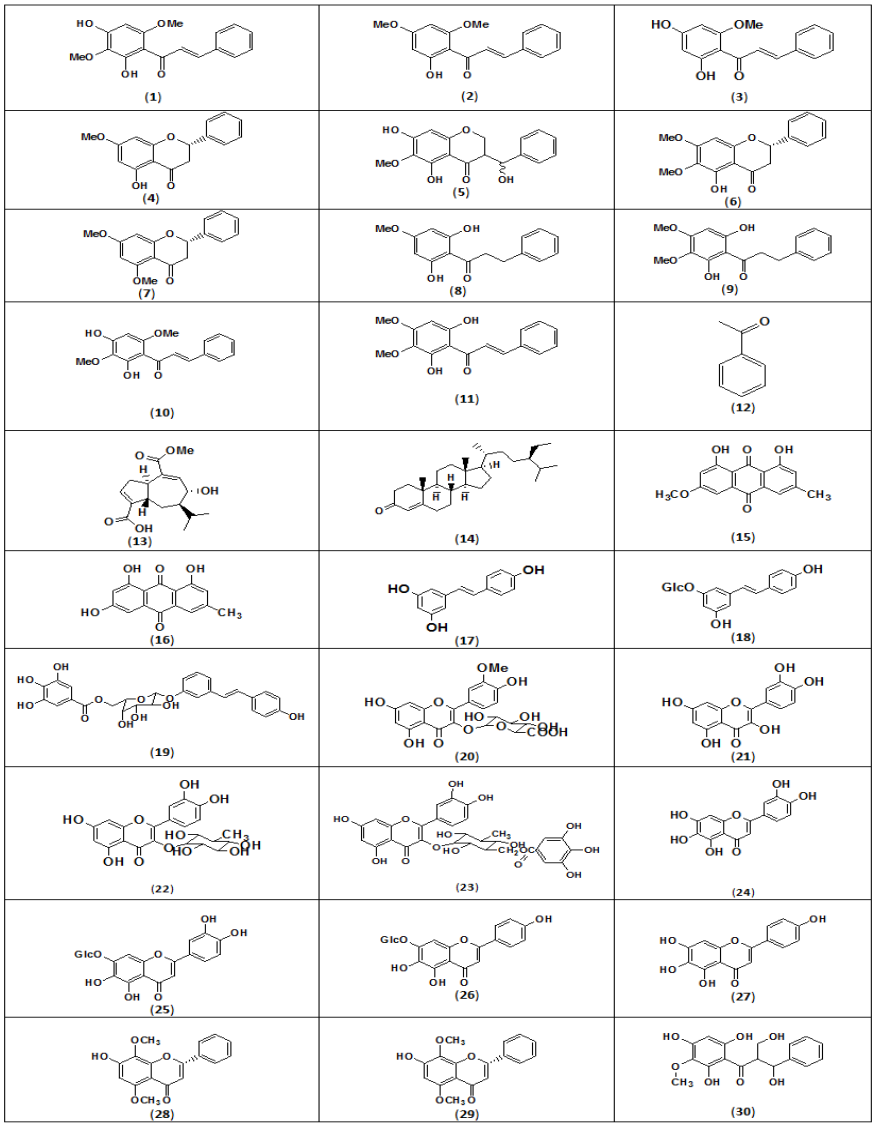

Fig. 1. Some bioactive compounds obtained from the *Polygonum* genus. (1) 2',4'-dihydroxy-3',6'-dimethoxychalcone; (2) 2'-hydroxy-4',6'-dimethoxychalcone; (3)cardamomin; (4)(S)-(-)-pinostrobin; (5) (±)-polygohomoisoflavanone; (6) (2S)-(-)-5-hydroxy-6,7-dimethoxyflavanone; (7) (2S)-(-)-5,7-dimethoxyflavanone; (8) 2',6'-dihydroxy-4'-methoxydihydrochalcone; (9) 2',6'-dihydroxy-3',4'-dimethoxydihydrochalcone; (10) 2',4'-dihydroxy-3',6'-dimethoxychalcone;(11) 2',6'-dihydroxy-3',4'-dimethoxychalcone; (12)acetophenone ; (13)viscozulenic acid ; (14) sitosterone; (15) physcion; (16) emodin; (17) resveratrol; (18) polydatin; (19) resveratrol 4-O-D-(2'-galloyl)-glucopyranoside; (20) quercetin 3-O-β-D-glucuronide; (21) quercetin; (22)quercitrin; (23) galloyl kaempferol 3-glucoside; (24) kaempferol 3-glucoside; (25) 6-Hydroxyluteolin; (26) 6-Hydoxyluteolin 7-O'-D-glucopyranoside; (27) 6-Hydroxyapigenin; (28) scutillarein; (29) 5.8-dimethoxy-7-hydroxyflavanone;(30) homoferrugen-dihydrochalcone

Emodin also exerted cytotoxic effects against human prostate cancer cell LNCaP, glioma cells [33] and human chronic myelocytic leukemia K562 cells [34]. The anticancer activities of the crude extract, fractions and flavonoids isolated from *Polygonum limbatum* were studied [7]. In experiment, the cytotoxicity of samples studied on several cancer cells such as breast carcinoma MCF-7, Leukemia THP-1, prostate carcinoma PC-3, Lung A549, cervical carcinoma HeLa. The

results showed that, more than 50% inhibition of the proliferation was observed on above cell lines except Lung A549. Cardamomin and 2',4'-dihydroxy-3',6'-dimethoxychalcone are very active against THP-1 cell with IC_{50} below 4 $\mu g.mL^{-1}$ [7]. Furthermore, the cytotoxicity of crude extracts and compounds from *Polygonum spectabile* were also evaluated [22,35]. The cytotoxicity of crude extracts and compounds such as 2'-hydroxy-4',6'-dimethoxychalcone, 2',4'-dihydroxy-3',6'-dimethoxychalcone and 3-O-*β*-D-glucosyl-*β*-sitosterol (500-0.125 $\mu g.mL^{-1}$) to Vero and LLCMK2 cells were evaluated by using MTT assay. Each test was carried out in four replicates with at least four different concentrations. The results revealed that the three compounds isolated from *P. spectabile* showed moderate *in vitro* cytotoxicity activity against Vero and LLCMK2 cells with CC_{50}<50 $\mu g.mL^{-1}$ [35].

5.2 Antioxidant and Free Radical Scavenging Effects

The antioxidant effect of *Polygonum chinense* extract was evaluated. In this experiment, the preventive effects of aqueous extract against gastric mucosal injury in rats were determined [36]. The result of study showed that this extract significantly protects gastric mucosal [36]. The anti-ulcer activity of aqueous extract of *Polygonum minus* against gastric ulcer was also investigated. The results revealed that the plant extract induced a marked reduction in edema and conferred gastric protection [37]. Moreover, the toxicity of *P. minus* was studied. The higher dose (5 $g.kg^{-1}$) did not show any toxicological sign in rats [37]. The antioxidant effects of some *Polygonum* species have been examined by Hsu and coworkers. In this experiment, the ethanol extract of the root of *P. cuspidatum* was used as sample and evaluated the antioxidant activities, free radical scavenging, superoxide radical scavenging, lipid peroxidation assays have been used and IC_{50} values have been respectively obtained; 110 $mg.g^{-1}$, 3.2 $mg.g^{-1}$ and 8 $mg.g^{-1}$. Furthermore, the extract of this plant had a DNA-protective activity. The results indicated that *P. cuspidatum* extract had antioxidant activities [38]. In another experiment in 1993, in fact, Jin and coworkers evaluated the antioxidant activity of polydatin (3.2, 6.4, 12.8 and 25.6 $\mu mol.l^{-1}$), a molecule isolated from *P. cuspidatum* extract. Polydatin also showed a strong potential to scavenge oxygen free radicals with IC_{50} = 14.6 $\mu mol.L^{-1}$ for superoxide radicals (O^{2-}), hydroxyl radicals (OH^{-}) (IC_{50} = 29.6 $\mu mol.l^{-1}$) and hydrogen peroxide (H_2O_2) (IC_{50} = 13.0 $\mu mol.L^{-1}$) [39].

The *in vitro* antioxidant activity of *P. barbatum* extract was investigated by different strategies including hydroxyl radical scavenging assay, DPPH radical scavenging assay, superoxide scavenging assay, nitric oxide scavenging assay and total phenolic content. The IC_{50} (32.62 $\mu g.ml^{-1}$) value found in the DPPH radical scavenging method was higher than with other methods. *P. barbatum* extract contained phenolic compounds, which showed significative antoxidant effects [39]. The *in vitro* studies clearly showed that the ethanolic extract of *P. barbatum* is a new source of natural antioxidants that might prevent and control the process of oxidative stress [39].

5.3 Anti-inflammatory Effects

In 2008, one American research team studied the anti-inflammatory effects of *P. cuspidatum*. In this experiment, the plant material was extract with ethanolic solution and use as sample. The study evaluated the ability of sample to inhibit animal (mouse) ear inflammation. Sample was applied to both ears of animals at different doses 0.075, 0.15, 0.3, 1.25 and 2.5 $mg.ear^{-1}$ 30 min after topical application of 12-*O*-tetradecanoylphorbol-13-acetate administration (2 $\mu g.ear^{-1}$). Comparing to the topical application of 12-*O*-tetradecanoylphorbol-13-acetate as control, sample treatment at different doses siginficantly decreased ear edema. Myeloperoxidase effect was inhibited at *P. cuspidatum* extract doses ≥ 1.25 $mg.Kg^{-1}$. Trans-resveratrol also inhibit inflammation at different comparables doses. The development edema is inhibited by the extract of *P.cuspidatum* [40].

5.4 Wound Healing Effects

After wound treatment, a scar often forms, yielding an unpleasant spot. It is therefore necessary to erase the scar to regain the original luster. Based on multiple activities of plants of the genus *Polygonum*, the wound healing activity of *P. barbatum* was evaluated. Ethanol and water were used as solvent to extract the whole plant [41]. Excision and incision were two wound models used to study this effect. The extracts responded significantly (P<0.001) in both the wound models tested. Between the two extracts, the aqueous extract was more active than the ethanol extract [41].

5.5 Anti Allergic Effects

The anti allergic activity of *P. cuspidatum* radix extract was investigated by Lim and co-workers [42]. In this experiment, the extract was tested against two different mast cells and the sample showed very potent inhibitory effect with IC_{50} values (62±2.1) $\mu g.ml^{-1}$ for RBL-2H3 and (46±3.2) $\mu g.mL^{-1}$ for bone marrow–derived mast cells by antigen stimulation. The extract also exhibited the ability to supress the expression of interleukin-4 in RBL-2H3 cells and tumor necrosis factor-α. Concerning the *in vivo* animal allergy model, in dose dependent manner, *P.cuspidatum* radix inhibited passive cutaneous anaphylaxis, a local allergic reaction. The same sample also showed significative inhibition to activate phosphorylation of Syk and expressed the ability to suppress the mitogen-activated protein kinases ERK1/2 [42].

5.6 Anti Molluscidal and Antiplasmodial Effects

The anti molluscidal activity of crude aqueous and methanol extracts and compounds from *Polygonum senegalense* was evaluated [43] and the samples showed significative molluscidal effect against two different strains snails (*Biomphalaria pfeifferi* and *Biomphalaria sudanica*). One of compounds namely 2',4'-dihydroxy-3',6'-dimethoxychalcone was very active with 100% lethal to both snails in less tahn six hours. Two other fractions (hydrophobic and hydrophylic) of methanol extract of this plant also showed molluscidal activity on these snails [43]. Furthermore, the *in vitro* antiplasmodial activity of extract and compounds (polygohomo isoflavanone (19.2±0.6) µM for D6 and (18.2±1.8 µM), 2'- hydroxy- 4',6'- dimethoxychalcone (15.7±1.2 µM) for D6 and (11.3±0.2 µM) for W2 and 2',6'- dihydroxy- 3',4'- dimethoxychalcone (3.1±0.8 µM) for D6 and (2.4±0.3 µM) from *P. senegalense* was evaluated against two strains of *Plasmodium falciparum* (D6 and W2). The result showed that compounds isolated from *P. senegalense* are significantly active with IC_{50} between (19.2 to 2.4 µM) against two strains (D6 and W2) malaria parasite [44].

5.7 Antibacterial and Antifungal Effects

Several experiments have documented the antibacterial and antifungal potential of extracts and compounds from the genus *Polygonum*. The extract and compounds isolated from *Polygonum spectabile* were also evaluated for their effects on 15 bacteria. Hydrophylic extracts of *P. spectabile* were active against *Staphylococcus aureus, Bacillus subtillis, Micrococcus luteus, Micrococcus canis, Trichophyton mentagrophytes* and *Trichophyton rubrum*. The results indicated that the use of *P. spectabile* may act as an antibacterial and antifungal agent [35]. Another antimicrobial screening of ethanol leaf extract of *P. barbatum* was assessed on ten microorganisms which include four Gram-positive, four Gram-negative bacteria and two fungi. The ethanol leaf extract showed considerable activity on both the bacteria and fungi, with inhibition zone diameter ranging from 14.17 to 31.45 mm and the minimum inhibitory concentrations ranging from 12 to 16 $\mu g.mL^{-1}$. These results showed that the ethanol extract of this plant is a broad-spectrum antimicrobial agent which can be used against Gram-positive and -negative bacteria and also against fungi [39].

The antimicrobial activities of *P. cuspidatum* were also investigated [45]. In this experiment, the aqueous extract of *P. cuspidatum* (1.0 $g.mL^{-1}$) showed antibacterial activity against *Staphylococcus aureus, Staphylococcus albus, Escherichia coli, α–Streptococcus, β–Streptococcus, Bacterium typhosum and Pseudomonas aeruginosa*; the inhibition zones were 1.122, 1.113, 1.127, 0.800, 0.929, 0.903,1.112 cm, respectively [46]. The methanol extracts of this plant also exhibited antibacterial activities against *Streptococcus sobrinus* and *Streptococcus mutans* at the minimum inhibitor concentration (MIC) (0.5–4 $mg.mL^{-1}$). This result suggested that the methanol extract could be used to control dental plaque and dental caries formation [6,47]. In another experiment, the crude extract of *P. cuspidatum* was tested against five common foodborne bacteria. The sample exhibited antibacterial activities against *Bacillus cereus*, *S. aureus* and *Listeria monocytogenes* at the minimum inhibitor concentrations of 312.5, 312.5 and 156.3 $\mu g.mL^{-1}$ respectively, and the bactericidal minimum inhibitor concentrations were 625, 1250 and 312.2 $\mu g.mL^{-1}$ [48]. In 2010, the antibacterial activities of methanol extract and fractions of *P. cuspidatum* on the development of dental caries were re-investigated. The results of the experiment showed that the ethyl acetate fraction, constituted mainly of polydatin, resveratrol, emodin and anthraglycoside B, exhibited significant antibacterial activities against eight different strains of *Streptococcus*, including *Streptococcus sobrinus* KCTC 3388, *S.*

mutans from different strains (KCTC 3308, KCTC 3307, KCTC 3389, KCTC 3306, KCTC 3300, KCTC 3298) and *Streptococcus cricetus* KCTC 3292, with minimum inhibitor concentrations of 0.5, 1, 0.5, 1, 0.5, 0.5, 0.125 and 0.25 $mg.mL^{-1}$ respectively, and minimum bactericidal concentrations of 2, 4, 2, 2, 2, 1, 2, 0.5 $mg.mL^{-1}$ respectively [49].

5.8 Genotoxicity Effects

Genotoxicity is a destructive effect on a cell's genetic material (DNA, RNA) affecting its integrity. *Polygonum multiflorum* has been designed for its potential to control genotoxicity. In this context, Zhang and coworkers studied genotoxicity in mouse peripheral lymphocyte cells with the use of *Panax ginseng* and *P. multiflorum* and the activity of their combination [50]. They administered them individually or in combination, on mouse peripheral lymphocyte DNA. *P. multiflorum* and its combination with *Panax ginseng* were orally administered to mice at gradient doses (low, medium and high) for seven consecutive days. On the first, third and seventh days, two hours after drug administration, blood samples were collected from the vein cluster behind the eye. *Panax ginseng* (0.43, 1.3 and 3.9 $g.kg^{-1}$) was found to have no harmful effects on peripheral lymphocyte DNA. *P. multiflorum* (3.9 and 11.7 $g.kg^{-1}$), on the other hand, had harmful effects on peripheral lymphocyte DNA on the first, third and seventh days. The combination of both plants (5.2 and 15.6 $g.kg^{-1}$) induced harmful effects on peripheral lymphocyte DNA on the first day, as showed in tail DNA tail length. Nevertheless, these harmful effects decreased on the third and seventh days. The results showed that the combination of these two plants may be used to control potential genotoxic effects and this activity is induced by *P. multiflorum* [50].

5.9 Hepatotoxicity Effects

Several experiments investigated the *in vitro* and *in vivo* hepatoxicity of hot-water-extracts of *P. multiflorum* in mice [51]. After treating primary cultured hepatocytes with *P. multiflorum* extracts at three final concentrations (0.5, 1.0 and 5.0 $mg.mL^{-1}$) with or without acetaminophen (10 mM) for 24 h, no cytotoxic effects was observed. Cell viability and lactate dehydrogenase leakage were significantly improved at the highest *P. multiflorum* extract dose compared with controls. Mice that received the *P. multiflorum* extracts (20 or 340 mg extracts/mouse x 2) orally administered twice daily for 10 days indicated no unfavorable effect on the liver function. When the mice sub-chronically received the higher dose of *P. multiflorum* extract (340 mg) before the treatment with a single-bolus dose of acetaminophen (500 $mg.kg^{-1}$), attenuation of acetaminophen-induced hepatotoxicity was significantly *in vivo* established [51]. The results showed that *P. multiflorum* does not induce any toxicological effect on the liver and may in fact elicit useful but limited beneficial effects on the liver *in vivo* [51].

5.10 Antiviral Effects

An antiviral activity, an important and specific effect of *P. cuspidatum* was extensively investigated. Several experiments have shown that crude extracts or compounds isolated from *P. cuspidatum* have ability to control HIV [26,52,53]. In 1998, Jiang and coworkers evaluated the antiviral effect of water extract of this plant (50 mg/mouse/day, for 1 month); the sample exhibited an antiviral activity in an HIV-infected murine model [52]. Several compounds such as resveratrol, catechin, 5,7-dimethoxyphthalide and emodin 8-*O*-*β*-D-glycopyranoside isolated from *P. cuspidatum* showed significant antiviral activity against HIV-1; EC_{50} values were 4.37±1.96 $\mu g.ml^{-1}$, 14.4±1.34 $\mu g.ml^{-1}$, 19.97±5.09 $\mu g.ml^{-1}$ and 11.29±6.26 $\mu g.ml^{-1}$ respectively [26]. In addition, resveratrol was also considered as a new molecule for anti-HIV therapeutics [53]. In fact, resveratrol pretreatment dose-dependently increased sirtuins 1 protein expression and intracellular NAD+ level. This compound and the extract of *P. cuspidatum* were used against Epstein-Barr virus (EBV) [54], hepatitis B virus (HPV) [55].

6. PHARMACOKINETICS

Plants from the *Polygonum* genus have many pharmacological effects, including anticancer, antioxidant and free radical scavenging, anti-inflammatory, wound healing, anti allergic, anti molluscidal, antiplasmodial, antibacterial, antifungal, genotoxic, hepatotoxic and antiviral effects. From these biological activities it can be noted that several extracts and pure compounds isolated from *Polygonum* genus plants have a promising future to control, prevent various pathogenics. The preliminary results suggest the viability of future investigations, such as studies involving the mechanisms of action, pharmacokinetics and pharmacodynamics of these pure compounds.

Table 1. Pharmacological effects of some extracts and compounds isolated from some *Polygonum*

Plants	Extracts. compounds	Pharmacological effects	Minimal active concentration.dose	*In vivo. in vitro*	Reference
Polygonum spectabile	Hexane extract	*Anti-Tricophyton mentagrophytes*	18.5±0.8 mg.disc^{-1}	*In vitro*	[35]
		Anti-Tricophyton rubrum	10.5±1.1 mg.disc^{-1}	*In vitro*	
		Anti-Micrococcus canis	9.5±1.4 mg.disc^{-1}	*In vitro*	
		Anti-Vero cells	83.6±4.6 µg.ml^{-1}	*In vitro*	
		Anti- LLCMK$_2$Cells	71.3±3.5µg.ml^{-1}	*In vitro*	
	Dichloromethane extract	*Anti-Tricophyton mentagrophytes*	11.5±0.8 mg.disc^{-1}	*In vitro*	[35]
		Anti-Tricophyton rubrum	10.5±0.5 mg.disc^{-1}	*In vitro*	
		Anti-Micrococcus canis	8.5±0.9mg.disc^{-1}	*In vitro*	
		Anti-Vero cells	128.2±6.9µg.ml^{-1}	*In vitro*	
		Anti- LLCMK$_2$Cells	117.9±7.2µg.ml^{-1}	*In vitro*	
	Ethyl acetate extract	*Anti-Staphylococcus aureus*	8.8±0.8 mg.disc^{-1}	*In vitro*	[35]
		Anti-Tricophyton mentagrophytes	12.0±0.9 mg.disc^{-1}	*In vitro*	
		Anti-Tricophyton rubrum	9.5±0.6 µg.ml^{-1}	*In vitro*	
	Ethanol extract	*Anti-Staphylococcus aureus*	7.5±0.5 µg.ml^{-1}	*In vitro*	[35]
		Anti-Micrococcus luteus	9.5±0.5 µg.ml^{-1}	*In vitro*	
		Anti-HHV-1[a]	21.9±1.8µg.ml^{-1}	*In vitro*	
	2'-hydroxy-4',6'-dimethoxychalcone	*Anti-Staphylococcus aureus*	15.2±0.9 mm	*In vitro*	[35]
		Anti-Staphylococcus epidermides	11.3±0.5 mm	*In vitro*	
		Anti-Bacillus subtillus	12.7±0.8 mm	*In vitro*	
		Anti-Micrococcus luteus	11.3±0.5 mm	*In vitro*	
		Anti-Micrococcus canis	14.6 mm	*In vitro*	
		Anti-Tricophyton mentagrophytes	24.7 mm	*In vitro*	
		Anti-Tricophyton rubrum	24.3 mm	*In vitro*	
	2',4'-dihydroxy-3',6'-dimethoxychalcone	*Anti-Vero cells*	31.5 µg.mL^{-1}	*In vitro*	[35]
		Anti- LLCMK$_2$Cells	29.6 µg.mL^{-1}	*In vitro*	
	3-O-β-D-glucosyl-β-sitosterol	*Anti-Vero cells*	27.2 µg.mL^{-1}	*In vitro*	[35]
		Anti- LLCMK$_2$Cells	7.8 µg.mL^{-1}	*In vitro*	
Polygonum limbatum	cardamomin	*Anti-THP-1 (Leukemia)*	1.8 µg.mL^{-1}	*In vitro*	[7]
		Anti-Hela (cervix)	17 µg.mL^{-1}	*In vitro*	
		Anti-PC-3 (prostate)	49 µg.mL^{-1}	*In vitro*	
		Anti-MCF-7 (breast)	32 µg.mL^{-1}	*In vitro*	

Plants	Extracts. compounds	Pharmacological effects	Minimal active concentration.dose	*In vivo. in vitro*	Reference
	(±) Polygohomoisoflavanone	*Anti-THP-1 (Leukemia)*	32.5 µg.mL^{-1}	*In vitro*	[7]
		Anti-PC-3 (prostate)	40 µg.mL^{-1}	*In vitro*	[7]
		Anti-MCF-7 (breast)	36 µg.mL^{-1}	*In vitro*	[7]
	2',4'-dihydroxy-3',6'-dimethoxychalcone	*Anti-THP-1 (Leukemia)*	3.5µg.mL^{-1}	*In vitro*	[7]
		Anti-Hela (cervix)	22 µg.mL^{-1}	*In vitro*	[7]
	(S)(-)-pinostrobin	*Anti-THP-1 (Leukemia)*	9 µg.mL^{-1}	*In vitro*	[7]
		Anti-PC-3 (prostate)	40 µg.ml^{-1}	*In vitro*	[7]
		Anti-MCF-7 (breast)	36 µg.mL^{-1}	*In vitro*	[7]
	(2S)-(-)-5-hydroxy-6,7-dimethoxyflavanone	*Anti-THP-1 (Leukemia)*	25.5 µg.m^{-1}L	*In vitro*	[7]
		Anti-MCF-7 (breast)	47 µg.mL^{-1}	*In vitro*	[7]
	(2S)-(-)-5,7-dimethoxyflavanone	*Anti-THP-1 (Leukemia)*	10 µg.mL^{-1}	*In vitro*	[7]
		Anti-MCF-7 (breast)	37 µg.mL^{-1}	*In vitro*	[7]
	Methanol extract	*Anti-THP-1 (Leukemia)*	10 µg.mL^{-1}	*In vitro*	[7]
		Anti-PC-3 (prostate)	28 µg.mL^{-1}	*In vitro*	[7]
		Anti-MCF-7 (breast)	20 µg.mL^{-1}	*In vitro*	[7]
	n-Butanol extract	*Anti-THP-1 (Leukemia)*	9 µg.mL^{-1}	*In vitro*	[7]
		Anti-PC-3 (prostate)	9 µg.mL^{-1}	*In vitro*	[7]
		Anti-MCF-7 (breast)	18 µg.mL^{-1}	*In vitro*	[7]
	Ethyl acetate extract	*Anti-THP-1 (Leukemia)*	8.5 µg.mL^{-1}	*In vitro*	[7]
		Anti-MCF-7 (breast)	23 µg.mL^{-1}	*In vitro*	[7]
Polygonum cuspidatum	Ethanol extract	*Anti-inflammatory(reduced ear edema induced by TPA)*	0.075 mg.ear^{-1}	*In vivo*	[40]
		Anti-inflammatory(reduced myeloperoxidase activity)	2.5 mg.ear^{-1}	*In vivo*	[40]
	polydatin	*Inhibits the vasoconstrictive effect*	1.71 mmol.L^{-1}	*In vivo*	[60]
		Reduce lipogenesis of rats	50 mg.kg^{-1}	*In vivo*	[61]
		Enhanced MCF-7 proliferation	20 µmol.L^{-1}	*In vitro*	[62]
	physcion	*Inhibition of melanogenesis effect*	10 µmol.L^{-1}	*In vitro*	[63]
	emodin	*Inhibition of melanogenesis effect*	10 µmol.L^{-1}	*In vitro*	[63]
		Anti-HSV-1	4 mg.mL^{-1}	*In vivo*	[64]
		Anti-human chronic myelocytic leukemia K562 cells	25 µmol.L^{-1}	*In vitro*	[34]
		Anti-human prostate cancer cells	10 µmol.L^{-1}	*In vitro*	[65]

Plants	Extracts. compounds	Pharmacological effects	Minimal active concentration.dose	*In vivo. in vitro*	Reference
		Anti-glioma cells	100 µmol.L^{-1}	*In vitro*	[66]
	cytreosein	*Inhibition of melanogenesis effect*	10 µmol.L^{-1}	*In vitro*	[63]
	anthraglycoside	*Inhibition of melanogenesis effect*	10 µmol.L^{-1}	*In vitro*	[63]
	Water extract	*Anti-Escherichia coli*	1 g.mL^{-1}	*In vitro*	[46]
		Anti-Bacterium typhosum	1 g.mL^{-1},	*In vitro*	[46]
		Anti-pseudomonas aeruginosa	1 g.mL^{-1}	*In vitro*	[46]
		Anti-Staphylococcus aureus	1 g.mL^{-1},	*In vitro*	[46]
		Anti-Staphylococcus albus	1 g.mL^{-1}	*In vitro*	[46]
		Anti-α-Streptococcus aureus	1 g.mL^{-1}	*In vitro*	[46]
		Anti-β-Streptococcus	1 g.mL^{-1}	*In vitro*	[46]
	resveratrol	*Anti-tumor*	40 mg.kg^{-1}	*In vivo*	[24]
		Anti-uveal melanoma tumors	20 mg.tumor.times^{-1}	*In vivo*	[32]
		Anti-human neuroblastomas	5 mg.tumor.times^{-1}	*In vivo*	[32]
		Anti-lymph cancer	100 µmM	*In vitro*	[28]
		Anti-atypical teratoid tumors	150 µM	*In vitro*	[33]
	resveratrol	*Anti-hepatic cancer*	12.5 µM	*In vitro*	[38]
	resveratrol	*Anti-EBV*	13.8 µM	*In vitro*	[54]
Polygomun senegalense	2',6'-dihydroxy-4'-methoxydihydrochalcone	*Anti-D6 plasmodium falciparum*	23.5 µM	*In vitro*	[44]
		Anti-W2 plasmodium falciparum	22.8 µM	*In vitro*	[44]
	2',6'-dihydroxy-3',4'-dimethoxydihydrochalcone	*Anti-D6 plasmodium falciparum*	11.8 µM	*In vitro*	[44]
		Anti-W2 plasmodium falciparum	12. µM	*In vitro*	[44]
	2',4'-dihydroxy-3',6'-dimethoxychalcone	*Anti-W2 plasmodium falciparum*	17.8 µM	*In vitro*	[44]
		Anti-D6 plasmodium falciparum	16.6 µM	*In vitro*	[44]
Polygonum Barbatum	Acetophenone	*Anti-DPPH*	1.8 x 10^{-1}mg.mL^{-1}	*in vitro*	[67]
	Viscozulenic acid	*Anti-DPPH*	1.2X10^{-1}mg.mL^{-1}	*In vitro*	[67]
	Sitosterone	*Anti-DPPH*	2.1X10^{-1}mg.mL^{1}	*In vitro*	[67]
Polygonum hydropiper	Quercetin 3-*O*-*β*-D-glucuronide	*Antioxidant*	5.08 (TEAC value)	*In vitro*	[13]
	Quercetin	*Antioxidant*	4.65(TEAC value)	*In vitro*	[13]
	Quercitrin	*Antioxidant*	3.46 (TEAC value)	*In vitro*	[13]
	Galloyl kaempferol 3-glucoside	*Antioxidant*	2.90 (TEAC value)^{1}	*In vitro*	[13]
	Kaempferol 3-glucoside	*Antioxidant*	1.39 (TEAC value)	*In vitro*	[13]
	6-Hydroxyluteolin	*Antioxidant*	2.33 (TEAC value)	*In vitro*	[13]
	6-Hydoxyluteolin 7-*O'*-D-	*Antioxidant*	2.87 (TEAC value)	*In vitro*	[13]

Plants	Extracts. compounds	Pharmacological effects	Minimal active concentration.dose	*In vivo. in vitro*	Reference
	glucopyranoside				
Polygonum ferrugineum	5.8-dimethoxy-7-hydroxyflavanone	*Anti-Trichophyton mentagrophytes ATCC9972*	250 µg.mL^{-1}	*In vitro*	[68]
		Anti-Trichophyton rubrum CCC113	250 µg.mL^{-1}	*In vitro*	[68]
		Anti-Epidermophyton floccosum CCC114	250 µg.mL^{-1}	*In vitro*	[68]
	Homoferrugen-dihydrochalcone	*Anti-Trichophyton mentagrophytes ATCC9972*	200 µg.mL^{-1}	*In vitro*	[68]
		Anti-Trichophyton rubrum CCC113	250 µg.mL^{-1}	*In vitro*	[68]
	Methanol extract	*Microsporum gypseum CCC 115*	125 µg.mL^{-1}	*In vitro*	[68]
		Anti-Trichophyton rubrum CCC113	50 µg.mL^{-1}	*In vitro*	[68]
		Anti-Trichophyton mentagrophytes ATCC9972	125 µg.mL^{-1}	*In vitro*	[68]
		Anti-Epidermophyton floccosum CCC114	50 µg.mL^{-1}	*In vitro*	[68]

Furthermore, a few pharmacokinetic investigations have been done on *Polygonum* plants. In 2008, one pharmacokinetic experiment with rats received the extract of *P. cuspidatum*. After this experiment, methanol was used as polar organic solvent to extracted tissues and solid-phase extraction was used to clean urinary and bilary samples. The secondary metabolites were analyzed and identified in mass spectrometry. The major of the chemical constituents of this extract was resveratrol, which was distributed in the liver, kidney, duodenum and stomach [56]. With this result, other scientists then evaluated different active compounds of *P. cuspidatum*. In particular, emodin was investigated in rats using selective HPLC method. The result of this experiment clearly showed that emodin is quickly absorbed into the blood stream and rapidly transferred into the liver [57]. In 2012, the results of experiments using a HPLC method showed that after oral administration of *Polygonum cuspidatum* extract, glucuronides or sulfates of resveratrol and emodin were the best forms in distribution and organs [58,59].

7. TOXICOLOGY

Plants from the *Polygonum* genus have long been used as an important medicinal plant in the world. Some of these plants are traditionally considered to be toxic, such as *P. cuspidatum*, which according to Chinese folk medicine, the plant induces abortion and for this reason, it's prohibited for pregnant women [5]. The aqueous extract of *Polygonum minus* was administrated orally in rats with 5 $g.kg^{-1}$ (higher dose), the acute toxicity was studied and animals model did not present toxicological signs [37]. It was also reported that LD_{50} of emodin (249.5±34.3 $mg.kg^{-1}$) and polydatin (1000±57.3 $mg.kg^{-1}$) were (249.5±34.3 $mg.kg^{-1}$) administrated orally did not cause death in mice. In one acute toxicity study, rats were treated with the extract of *P. chinense* at a dose of 2 or 5 $g.kg^{-1}$. Despite the bad health of rats, no signs of toxicity have been observed at these doses. No abnormalities have been observed after biochemical serology and histological indicators of liver and kidney analysis [36].

8. CONCLUSION AND PROSPECTS

The present review covers many medicinal properties of some plants from the *Polygonum* genus, with further mechanism of actions and toxicity yet to be established. Studies on *Polygonum* plant extracts could be targeted to develop novel anticancer and anti allergic agents and potential antiplasmodial and anti-inflammatory drugs, from the active compounds [69]. These active principles could be clinically evaluated to develop therapeutic drugs with more safety, efficacy and tolerability. Apart from this, a new approach could be developed for preparing this herbal product, as well as in combination with other plants. Other pharmacological properties for use in artherosclerosis, neurological disorders, diabetes, hypertension and immunomodulatory effects should be evaluated. Moreover, in agriculture, the anti-nematode and anti-insecticidal activities of *Polygonum* plants extracts against potato pathogens will also be evaluated. In summary, data reviewed here clearly show the enormous potential of *Polygonum* plants for the development of new pharmaceuticals, adding this genus to the list of highly promising native compounds to undergo further research.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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