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Review

Herbal remedies as alternative to conventional therapies for the treatment of pediatric infectious diseases

Bahare Salehi[1], Reza Entezari Heravi[2], Zahra Eydian[3], Zorica Stojanovic-Radic[4], Miquel Martorell[5,6], Marcello Iriti[7*], Javad Sharifi-Rad[8*]

[1] Student Research Committee, School of Medicine, Bam University of Medical Sciences, Bam, Iran
[2] Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Zabol University of Medical Sciences, Zabol, Iran
[3] Department of Pediatrics, Zabol University of Medical Sciences, Zabol, Iran
[4] Department of Biology and Ecology, Faculty of Science and Mathematics, University of Niš, Višegradska 33, Niš, Serbia
[5] Department of Nutrition and Dietetics, Faculty of Pharmacy, and Centre for Healthy Living, University of Concepción, 4070386 Concepción, Chile
[6] Unidad de Desarrollo Tecnológico, Universidad de Concepción UDT, Concepción 4070386, Chile
[7] Department of Agricultural and Environmental Sciences, Milan State University, via G. Celoria 2, Milan 20133, Italy
[8] Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[*]**Correspondence to:** marcello.iriti@unimi.it; javad.sharifirad@gmail.com

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Abstract: Pediatric infections still represent a leading cause of mortality in many developing countries. Since ancient times, traditional healing systems provided some herbal remedies to treat pediatric diseases, only in some cases validated by an evidence-based approach. Therefore, this review covers the herbal remedies in Iranian traditional medicine and aims to assess the potential of phytotherapeutics as safe and effective alternatives to conventional therapies for the treatment of pediatric infectious diseases. Notably, pediatric patients may also benefit from adjuvant therapy, *i.e.,* combined treatment with herbal remedies and conventional therapies, to improve the efficacy of conventional drugs, decrease their adverse effects at the cell-tissue-organ-organism level and reduce the occurrence of microbial strains resistant to antibiotics. Therefore, traditional healing systems still represent an unlimited source of active ingredients to be tested in preclinical assays as well as in humans in terms of efficacy and safety.

Key words: Traditional healing systems; Iranian traditional medicine; Antibiotic resistance; Phytochemicals; Phytotherapeutics; Pediatric; Infectious diseases.

Introduction

According to World Health Organization (WHO), the infant mortality rate (IMR) is the number of deaths of infants less than one year old per 1,000 live births that can be used as an indicator of health quality in a country. Many factors such as the mother's level of education, social, economic and environmental conditions, as well as political and medical infrastructures, contribute to infant mortality. Improving sanitation, access to clean drinking water, immunization against infectious diseases, and other public health measures can help reduce high rates of infant mortality (1). The under-five mortality rate is the probability per 1,000 that a newborn will die before reaching age five. In 2015, an estimated 5.9 million children under the age of five died, and the global under-five mortality rate decreased by 53%, from 91 deaths per 1,000 live births, in 1990, to an estimated 43 in 2015 (2). According to the United Nations General Assembly, the year 2016 has marked the beginning of the implementation of the Sustainable Development Goals (SDGs). Under-five mortality rate less than 25 per 1000 live birth in every country around the world is the main goal of SDGs in 2030 (3). Of the 5.9 million under-five deaths in 2015, almost half died in the neonatal period, and the other deaths were caused by infectious diseases such as pneumonia, diarrhea, malaria, meningitis, AIDS, measles and conditions such as intrapartum-related events (2, 3). Among neonates, the leading causes of death were preterm birth complications, intrapartum-related events and sepsis or meningitis (3).

For many years, we had not enough data about drug therapies in the pediatric population. This problem has led to the use of empiric therapies in pediatrics hospitals, often guessing the treatment dose. In addition to this problem, we had no evidence about the safety and effectiveness of those drugs in this unique population (4). As children are among the most vulnerable population groups that contract illness around the world, there are many problems with medical treatment in this group. For example, erroneous use of antibiotics in first line treatment or prolonged administration of antibacterial in children leads to the emergence of resistant microbial strains. Also, generally, we have no evidence-based use or useful guidelines for traditional and herbal medicine to overcome pediatric diseases. In many low-income countries, much of the medicine supply is by-passing the conventional health care system. Treatment failure

due to the wrong dosage of drugs, non-availability of appropriate pediatric formulations, inappropriate packages, lack of awareness among parents and also cultural differences between countries around the world are other inevitable problems in children health care system (4, 5).

Many reports showed that the use of natural remedies for pediatric patients is high and that the interest of pediatricians in learning about them is increasing (6, 7). Herbal remedies and conventional therapeutics are most often used together, and the cultural background of each country can influence to decide the type of treatment by physicians (8). Similar to conventional therapeutics, herbal drugs are not completely safe, and their adverse effects on hospitalized children have been reported (9). A systematic review highlighted the paucity of data on the toxicity of herbal medicine in children (10). In this context, this review covers the herbal remedies in Iranian traditional medicine and aims to assess the potential of phytotherapeutics as safe and effective alternatives to conventional therapies for the treatment of pediatric infectious diseases.

Herbal remedies in Iranian traditional medicine

Plants and herbal remedies have been the basics of traditional medicinal systems worldwide for thousands of years to cure or prevent diseases. Because of low toxicity, efficacy, safety, tolerability and low adverse effects in comparison to conventional therapies, many people, in Iran, prefer to use natural remedies. Many herbal medicines such as *Punica granatum* L. (pomegranate), *Foeniculum vulgare* Mill. (fennel), *Mentha longifolia* (L.) L.(mint), *Allium sativum* L. (garlic), *Plantago* spp., *Glycyrrhiza glabra* L. (licorice) and *Rosa* × *damascena* Herrm. (Damask rose) have been used in Iranian traditional healing system (11-13). Many reports are available on the antiviral, antibacterial, antifungal, anthelmintic and anti-inflammatory properties of medicinal plants (14-21). For example, the use of *Arctostaphylos uva-ursi* (L.) Spreng. (bearberry) and *Vaccinium macrocarpon* Aiton (cranberry) juices to treat urinary tract infections is widely reported, while species such as *Melissa officinalis* L. (lemon balm), *A. sativum* and *Melaleuca alternifolia* (Maiden & Betche) Cheel (tee tree) are described as broad-spectrum antimicrobial agents (22, 23). *Hypericum scabrum* L., *Myrtus communis* L., *Pistacia atlantica* Desf., *Arnebia euchroma* (Royle) I.M.Johnst., *Salvia hydrangea* DC. ex Benth., *Satureja bachtiarica* Bunge, and *Thymus daenensis* Celak. are some examples of Iranian traditional herbal medicines that were investigated against *Escherichia coli*, *Bacillus cereus*, *Listeria monocytogenes* and *Candida albicans* (24).

In line with the spread of pediatric infectious diseases, plant extracts might represent a promising alternative in treating young patients (25). As previously, introduced, children are among the most vulnerable population groups, and the use of antimicrobials has become a routine practice in these patients (5). Noteworthy, herbal medicines can also decrease the adverse effects of conventional antibiotics and reduce the emergence of resistant microbial strains.

In the Iranian traditional healing system, some medicinal plants have shown antimicrobial effects and could be used as alternative treatments in pediatric infectious diseases (26-28). *Tordylium persicum* Boiss. & Hausskn., a species belonging to Apiaceae family, exhibited antimicrobial activity against *Staphylococcus aureus* the most common cause of musculoskeletal infections in pediatric patients. Additionally, methanolic extract of *T. persicum* showed to be effective against *Klebsiella pneumoniae,* which is a common nosocomial pathogen, especially in intensive care unit, and the leading cause of mortality from pneumonia in children under 5 years (27, 29).

Punica granatum L., known in Iran as "Golnar-e-Farsi," is another medicinal plant whose flowers are used as astringent, hemostatic, antibacterial, antifungal, antiviral and for treatment of bronchitis, diarrhea, digestive problems, dermal infected wounds and diabetes (30). *H. scabrum*, *M. communis*, *P. atlantica*, *A. euchroma*, *S. hydrangea*, *S. bachtiarica*, and *T. daenensis* are other examples of herbal medicines in Iran with antibacterial, antiviral and antifungal activities (31). However, more phytochemical studies will be necessary to determine and isolate the active constituents and evaluate the *in vitro* antimicrobial activity against a wide range of pathogenic microorganisms.

In human evidence: clinical studies

Clinical trials on traditional phytotherapeutics are of extreme importance to confirm their efficacy. However, clinical trials on children are less frequent than in adults, though, in many cases, they reported very promising and encouraging results. These studies investigated plant product efficacy in the treatment of a wide spectrum of health disorders, ranging from otitis media to diarrhea (Table 1). Nevertheless, in some cases, animal models should be preferable instead of using pediatric patients. Several reports of herbal toxicity was reported in children, such as the case-reported in three children's that presented life-threatening bradycardia, respiratory and central nervous system depression only minutes after taking large amounts of Jin Bu Huan tablets (7-60 tablets) (32), the encephalopathy reported in infants after oral intake of Neem tree oil (*Azadirachta indica* A.Juss.) (33), and the reported hepatitis in 15-year-old girl who takes *Teucrium chamaedrys* L. capsules (600 mg/day) for 2 months (34). However, the above cases are human negligence, not like the well-controlled studies discussed below.

Phytotherapeutics in pediatric respiratory disorders

Pelargonium sidoides DC. root extract was tested in several clinical trials on children. Matthys et al. (35) conducted an extensive study to evaluate the efficacy and safety of treatment with EPs 7630® (a drug preparation from the roots of *P. sidoides*) in 2099 patients (aged 0-93) with acute bronchitis. The results pointed to the very high potential of the tested herbal preparation, since a significant decrease in bronchitis severity score (BSS: cough, sputum, rales/rhonchi, chest pain at cough and dyspnea) was observed in all age groups, and especially in pediatric patients. Agbabiaka et al. (36) reviewed 6 randomized, controlled clinical studies demonstrating the safety and efficacy of EPs 7630 for

Table 1. Herbal remedies in pediatric disorders.

Plant/phytochemical	Dose	Biological activities	References
Respiratory disorders			
Pelargonium sidoides DC.	EPs 7630 three times daily 30 min prior to meal over a period of 14 days. 80 g EPs 7630 in 100 ml solution. Dosage: 10 drops (6 years or less), 20 drops (6-12 years) and 30 drops (>12 years).	Decrease acute bronchitis.	(35)
Pelargonium sidoides DC.	EPs 7630 three times daily over a period of 5 days. Dosage: 10 drops (1-5 years), 20 drops (6-12 years) and 30 drops (>12 years).	Decrease in cough frequency, nasal congestion and asthma attack frequencies.	(38)
Astragalus mongholicus Bunge, *Cordyceps sinensis* (fungi), *Stemonae* radix, *Fritillariae Cirrhosae* bulbus, and *Scutellariae* radix	CUF2, daily oral capsule over a period of 6 months. CUF2 capsule: 0.619 g of dried aqueous extract with an equal weight of five herbs.	No evidence to support the herbal formula in children with asthma.	(39)
Astragalus mongholicus Bunge, *Cordyceps sinensis* (fungi), *Stemonae* radix, *Fritillariae Cirrhosae* bulbus, and *Scutellariae* radix	CUF2, 6 daily oral capsules (3 g/day) over a period of 6 months.	Improved forced vital capacity and forced expiratory volume in 1 second in children with asthma.	(40)
Glycyrrhizae radix, *Sophora flavescens* Aiton radix, and *Ganoderma* (fungi)	ASHMI capsules (4 capsules, three times a day) over a period of 4 weeks. ASHMI capsule: 0.3 g dried aqueous extract.	Improvement observed in moderate-severe allergic asthma patients without adverse effect on adrenal function.	(41)
Glycyrrhizae radix, *Ophiopogonis* radix, *Panacis Quinquefolii* radix, *Pinellia ternata* (Thunb.) Makino, and *Tridacis procumbentis* herba	Modified Mai-Men-Dong-Tang herbal preparation, 40 or 80 mg/kg over a period of 4 months, in twice-daily dose (capsule weighed 400 mg).	Improvements in lung function and relieved asthma symptoms in patients.	(42)
Viola odorata L. flower	*Viola flower* syrup (12 g of dry flower in 100 mL), 2.5 mL or 5 mL three times per day for 2-5 and over 5 years old, respectively, for 5 days.	Effective in reduction and suppression of intermittent asthma caused cough	(44)
Laggera pterodonta (DC.) Sch.Bip. ex Oliv.	Three doses every 24 h for 5 days, 3 mL younger than 12 month and 5 mL aged 1-2 years (20% concentration).	Effective and safe to in hospitalized children with acute bronchiolitis.	(45)
Panax quinquefolius L.	600 mg (*American ginseng* extract) day 1, 400 mg day 2 and 200 mg day take it 3 times daily for a 3-day course.	Doses well tolerated and merit additional evaluation.	(46)
Skin disorders			
Ledeboiuriella seseloides, *Potentilla chinensis* Ser., *Anebia clematidis*, *Rehmannia glutinosa* (Gaertn.) DC., *Paeonia lactiflora* Pall., *Lophatherum gracile* Brongn., *Dictamnus albus* L., *Tribulus terrestris* L., *Glycyrrhiza uralensis* Fisch., and *Nepeta tenuifolia* Benth	8 weeks	Improvement of symptoms of non-exudative atopic eczema, with no evidence of hematological, renal or hepatic toxicities	(47)
Lonicerae flos, Menthae herba, Moutan cortex, Atractylodis rhizome, and Phellodendri cortex	3 daily oral capsules for 12 weeks	Improvement of quality life and reducing topical corticosteroid use in children with atopic dermatitis.	(48)
Lonicerae flos, Menthae herba, Moutan cortex, Atractylodis rhizome, and Phellodendri cortex	Syrup orally, twice day for 12 weeks	Improvement of the objective scoring atopic dermatitis, pruritus and children's dermatology life quality index scores 4 weeks after study completion	(49)
Other pediatrics disorders			
Atropine	Weekend atropine.	reduced severe amblyopia	(50)
Polyphenols	Bioactive polyphenols contained in solution. One day of dosing scale, based on patients' weight: 3.5 mL (10-19 kg), 7.0 mL (20-29 kg), 10.5 mL (30-39 kg), 14.0 mL (40-49 kg) and 17.5 mL (50-59 kg).	resolved acute diarrhea	(51)
Sterols	Daily yogurt-drink enriched with 2 g of plant sterols, 6-12 months.	Reduced LDL cholesterol	(52)
Echinacea purpurea (L.) Moench	Root and seed alcohol extract, 0.5 mL orally 3 times daily for 3 days at the onset of cold symptoms, followed by 0.25 mL orally 3 times daily for 7 more days.	Increased risk of having an episode of acute otitis media and inflammation episodes.	(53)

the treatment of acute respiratory infections in children and adults. In a systematic review and meta-analysis of randomized controlled trials, Timmer et al. (37) showed that *P. sidoides* preparations were effective in relieving symptoms of acute bronchitis in adults and children, and sinusitis in adults, while consistent data on other acute respiratory infections were not identified. Tahan and Jaman (38) investigated *P. sidoides* root extract EPs 7630 in the prevention of asthma attacks during viral infections in 61 children. Asthmatic children with viral upper respiratory tract infection were randomly subjected to daily treatment with EPs 7630 for five days. Although the intensity of fever and muscle aches did not differ among the groups, the results pointed to significantly different cough frequency, nasal congestion and asthma attack frequencies among treated and untreated groups (38).

Besides *P. sidoides*, other herbal preparations were investigated in children. Wong et al. (39) studied the efficacy of the herbal formula CUF2 in the improvement of clinical symptoms, biochemical markers of inflammatory response and immunomodulatory activity in children with asthma. The investigated herbal formula, used in Chinese traditional medicine, represented a dried aqueous extract obtained from 5 species in equal amounts (*Astragalus mongholicus* Bunge, *Cordyceps sinensis* (fungi), *Stemonae* radix, *Fritillariae Cirrhosae* bulbus, and *Scutellariae* radix). The double-blind trial included 85 children aged 7-15 years, which were randomly assigned to receive daily either oral herbal formula or placebo for 6 months. After completion of the trial, there was no significant difference between treated and placebo groups in all investigated parameters (dosage of steroids, disease severity score, lung function, expiratory flow rate, biochemical outcomes). Therefore, the authors concluded that there is no evidence to support the use of CUF2 in children with asthma (39). However, the same authors reported more encouraging results in another clinical trial on asthmatic children (40). The same formula was investigated on 90 children of the same age (7-15 years) as in the previous trial, during the same period (6 months) on two studies (placebo and treated) groups. This time, the results showed that herbal therapy improved two parameters of the lung function: forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), while steroid requirements remained the same between the two groups.

Another traditional Chinese medicine product, ASHMI (Anti-asthma herbal medicine intervention containing *Glycyrrhizae* radix, *Sophora flavescens* Aiton radix, and *Ganoderma* (fungi)), was administered in addition to standard therapy in a trial on asthmatic children aged 5-14 years. Patients were divided into 2 groups: one receiving standard inhaled corticosteroid therapy with the addition of ASHMI and one receiving inhaled corticosteroid treatment plus placebo. The results showed that, after 1 month, ASHMI was safe and well tolerated in children, and symptom scores improvement was higher in the ASHMI + standard group than in a standard alone group, particularly in the case of nasal symptoms (41).

In 100 children aged 5-18 years with asthma, Hsu et al. (42) investigated the efficacy of modified Mai-Men-Dong-Tang herbal preparation for mild to moderate asthma treatment. The herbal formula contained *Glycyrrhizae* radix, *Ophiopogonis* radix, *Panacis Quinquefolii* radix, *Pinellia ternata* (Thunb.) Makino, and *Tridacis procumbentis* herba. The patients were divided into 3 groups, one placebo and two active receiving 40 mg (40 patients) and 80 mg (40 patients) of the prepared herbal extract. After treatment, both active groups demonstrated a significant increase in FEV1 in comparison to the placebo group, but a dose-response related effect was not detected between the active groups (42).

In another study, a herbal formulation containing the previously mentioned Mai-Men-Dong-Tang formula (lacking *T. procumbentis* herba ingredient) was compared with traditional Lui-Wei-Di-Huang-Wan herbal formula (composed of the same herbs boiled) in the treatment of asthma (43). The not boiled herbal preparation, *i.e.,* Mai-Men-Dong-Tang, significantly reduced symptom scores, systemic steroid dose, total, and specific IgE levels. Therefore, boiling the same ingredients caused the loss of their anti-inflammatory activity (43).

Qasemzadeh et al. (44) studied the effect of *Viola odorata* L. flower syrup on the cough of 182 children aged 2 to 12 years with intermittent asthma. In this randomized study, the participants received *V. flower* syrup (12 g of dry flower in 100 mL of syrup) or placebo syrup (2.5 mL or 5 mL three times per day for 2-5 and over 5 years old, respectively) along with the salbutamol spray treatment (2 puff four times a day) for 5 days. The results showed that *V. flower* syrup acts as an adjuvant of short acting beta agonist and is effective in reduction and suppression of intermittent asthma caused cough.

Laggera pterodonta (DC.) Sch.Bip. ex Oliv. is a traditional Chinese medicine commonly used in respiratory tract infections. Shang et al. (45) evaluated the efficacy and safety of this plant (three doses every 24 h for 5 days) in 133 hospitalized children aged 3-24 months with acute bronchiolitis. The treatment provoked better responses on clinical severity score, respiratory rate, oxygen saturation, wheezing, and heart rate along with lower white blood cell and platelet counts, and aspartate aminotransferase.

In the study of Vohra et al. (46), safety and tolerability of ginseng extract were investigated on pediatric patients with upper respiratory tract infections. The study was designed as randomized, double blind, two doses plus placebo and was conducted on 46 patients 3-12 years of age. The study reported no serious adverse event among the three study groups (low dose, high dose and placebo group, 15 patients for each group). The study concluded that standard doses of ginseng were well tolerated in pediatric patients (46).

In summary, all mentioned trials demonstrated that some herbal preparations might be effective as complementary therapy in the treatment of pediatric respiratory disorders. Notably, plant formulas showed to be safe (without adverse effects) for children, even in the case of long-term treatment.

Phytotherapeutics in pediatric skin disorders

A number of trials have been carried to evaluate the efficacy of some traditional herbal remedies in improving the symptoms of extensive atopic dermatitis in children.

Traditional Chinese medicine treats atopic eczema

with decoctions prepared from different medicinal plants mixed in the specific formula, prepared by an experienced practitioner. In the study of Sheenan and Atherton (47), the active treatment containing *Ledebouriella seseloides*, *Potentilla chinensis* Ser., *Anebia clematidis*, *Rehmannia glutinosa* (Gaertn.) DC., *Paeonia lactiflora* Pall., *Lophatherum gracile* Brongn., *Dictamnus albus* L., *Tribulus terrestris* L., *Glycyrrhiza uralensis* Fisch., and *Nepeta tenuifolia* Benth. was investigated on 47 children (aged 1.5-18.1 years) with extensive non-exudative atopic eczema. Patients randomly received active treatment and placebo, each for 8 weeks with a 4-week wash-out period. The results demonstrated a significant improvement of symptoms in comparison to the placebo, with no evidence of hematological, renal or hepatic toxicities (47). When trial finished, these authors enrolled 37 children from the same group again and continued the same treatment up to 12 months. The results showed a 90% improvement in half of the treated children, while 7 of them were able to discontinue treatment without relapse. Because, even after long-term application, no significant toxicity was recorded, the authors concluded that this herbal formula might represent a therapeutic option for children with extensive atopic eczema unresponsive to conventional treatments (47).

In another study, Hon et al. (48) demonstrated that an oral administration of traditional Chinese herbal medicine is efficacy for the treatment of moderate-to-severe atopic dermatitis in 85 children aged 4-7 years. The treatment was to take 3 capsules (containing 5 plants: *Lonicerae* flos, *Menthae* herba, *Moutan* cortex, *Atractylodis* rhizome, and *Phellodendri* cortex) orally twice daily for 12 weeks and was efficacious in improving quality of life and reducing topical corticosteroid use in children with atopic dermatitis. The same authors (49) conducted another trial in 22 children (aged 4-7 years) suffering from moderate-to-severe atopic dermatitis investigating the efficacy of the traditional Chinese herbal in the form of syrup orally (twice daily for 12 weeks). The results showed improvements in the objective scoring atopic dermatitis, pruritus and children's dermatology life quality index scores 4 weeks after study completion.

Phytotherapeutics in other pediatric disorders

Pure phytochemicals have been investigated in pediatric patients too. In particular, atropine reduced severe amblyopia (50), polyphenols resolved acute diarrhea (51), and plant sterols significantly decreased LDL cholesterol levels in children (52).

To the best of our knowledge, only one study reported somewhat unexpected and negative effects of herbal treatment in pediatric patients. This was a randomized trial on children with recurrent otitis media, where the effects of *Echinacea purpurea* (L.) Moench treatment and osteopathic manipulative treatment (OMT) were investigated for the prevention of acute otitis media episodes (53). The study involved 90 children, aged 12-60 months with recurrent otitis media. During the trial, four groups received double placebo, *E. purpurea* plus placebo OMT, OMT (including cranial manipulation) plus placebo *E. purpurea*, or *E. purpurea* plus OMT. *E. purpurea* was administered in the form of a root and seed alcohol extract. The results showed that *E. purpurea* was associated with a borderline increased risk of having at least one episode of acute otitis media during 6-month follow-up compared to placebo. Therefore, otitis media prevention during cold treatment cannot be managed with *E. purpurea* in children, since this plant even increases the risk of acute inflammation episodes (53).

Phytochemicals with antimicrobial and antiviral activities

Bacterial and viral infections are the most important infectious diseases. Over 50 years of extensive researches have been carried out to achieve new antimicrobial drugs, but the emergence of multiple resistances in human pathogenic microorganisms, due to indiscriminate use of conventional antibiotics, forced scientists to search for new antimicrobials from various sources as medicinal plants (24, 54-57). Plant secondary metabolites include a plethora of bioactive phytochemicals not relevant for the plant growth and development but involved in environmental relationships such as the plant-microbe/pathogen interactions. Therefore, many phytochemicals possess antimicrobial activity and can be grouped into a number of classes (Figures 1 and 2).

Phenols

Phenolic acids consist of a single substituted phenolic ring with documented allelopathic activity against neighboring plants (58). In addition, it has been shown that phenols are toxic to microorganisms. The toxicity mechanism of phenolic compounds against microorganisms includes enzyme inhibition by the oxidized compounds, possibly through reaction with sulfhydryl groups. Enzyme inhibition can also occur through more nonspecific interactions with the proteins by hydroxyl groups in their phenolic structures (26). Carvacrol (Figure 1) is a monoterpenoid phenol present in a number of essential oils including those obtained from oregano, thyme, pepperwort, and wild bergamot. In *Pseudomonas aeruginosa*, it damages the bacterial cell membrane, also inhibiting the growth of other bacteria, e.g., *Escherichia coli* and *Bacillus cereus* (59, 60). Eugenol (Figure 1) is another phenolic compound found in clove essential oil and biostatic against both bacteria and fungi (61).

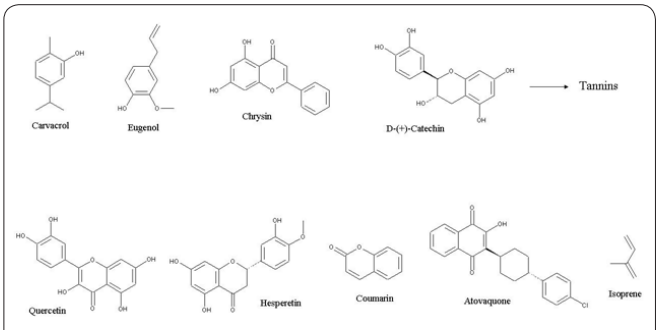

Figure 1. Phytochemicals relevant in pediatric infections include phenols (carvacrol and eugenol), flavonoids (chrysin, catechin, quercetin and hesperetin), condensed tannins or proanthocyanidins (arising from oligomerization or polymerization of catechin units), coumarins, quinones (atovaquone) and terpenes or isoprenoids (arising from the condensation of isoprene units).

Flavonoids

Flavonoids are hydroxylated polyphenolic compounds which have the general structure of a 15-carbon skeleton (The flavan nucleus) consisting of two phenyl rings and a heterocyclic ring(62, 63). Antimicrobial activity of flavonoids is probably due to their ability to complex with extracellular and soluble proteins as well as bacterial cell walls. Plants, in response to microbial infection or other biotic/abiotic stresses, synthesize them from the aromatic amino acid phenylalanine. Many *in vitro* and a limited number of *in vivo* studies showed that flavonoids have direct antibacterial activity, synergistic activity with antibiotics and the ability to suppress bacterial virulence factors (64-66). Catechins (Figure 1), flavonoids present in green tea, inhibited *in vitro Vibrio cholerae*, *Streptococcus mutans* and *Shigella flexneri* (67). Chrysin (Figure 1) was active against HIV, whereas quercetin and hesperetin (Figure 1) reduced the intracellular replication of herpes simplex virus type 1 (HSV-1), poliovirus type 1, parainfluenza virus type 3 and respiratory syncytial virus (68).

Coumarins

These compounds belong to the benzopyrone chemical class (Figure 1). Noteworthy, coumarins were used as precursors in the synthesis of anticoagulant drugs such as dicoumarol and warfarin. Coumarins were found to inhibit *Candida albicans in vitro*, stimulate macrophages and prevent recurrences of cold sores caused by HSV-1 in humans (26, 69).

Quinones

These compounds have aromatic rings with two ketone substitutions. Antimicrobial and antiparasitic effects of quinones were evaluated in many studies. For instance, atovaquone (Figure 1) an analog of ubiquinone, have been used for the treatment of *Pneumocystis pneumonia,* toxoplasmosis, and malaria (70).

Tannins

Condensed tannins or proanthocyanidins are polyphenolic compounds arising from the oligomerization or polymerization of catechin units (Figure 1), which play a role in plant protection from pathogens and phytophages, as well as in plant growth regulation. They form a complex with proteins by non-specific forces such as hydrogen bonding and hydrophobic interactions. Therefore, they can inactivate microbial adhesins, enzymes, membrane transport proteins and so on, acting as antimicrobial drugs. Clove, tarragon, cumin, thyme, vanilla, and cinnamon are plants rich in tannins (26, 71).

Terpenes

Terpenes or isoprenoids include a large and diversified group of chemicals derived from five-carbon isoprene units (Figure 1) assembled in different ways within the cell cytoplasm through the mevalonate pathway (72-75). These compounds contribute to the scents and colors of flowers and fruits, and, therefore, they are extensively used for their aromatic traits and medicinal properties (75). Bactericidal activity of terpenes has been documented against some bacteria such as *Listeria monocytogenes*, *Helicobacter pylori, Salmonella typhi, Staphylococcus aureus* and *Pseudomonas aeruginosa*

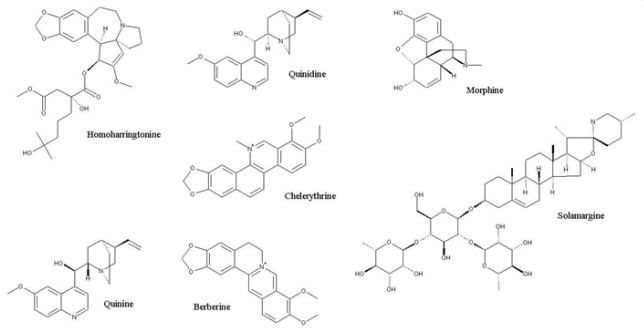

Figure 2. Alkaloids relevant in pediatric infections.

(76). Terpenes can penetrate and disrupt fungal cell wall, induce necrotic cell death and apoptosis through the mitochondrial pathway (77). In addition, many studies reported the antiviral activity of terpenes against HSV-1, cytomegalovirus and influenza viruses (32, 33).

Alkaloids

These are nitrogen-containing compounds arising from free amino acids(78). The first medically useful example of an alkaloid was morphine (Figure 2), isolated in 1805 from the opium poppy (*Papaver somniferum* L.) (26). Alkaloids have a wide range of pharmacological properties including anticancer (homoharringtonine), antiarrhythmic (quinidine), analgesic (morphine), antimalarial (quinine) and antibacterial (chelerythrine) activities (Figure 2) (79-82). Solamargine (Figure 2), which has been isolated from *Solanum americanum* Mill.*,* is a glycoalkaloid derived from the steroidal alkaloid solasodine active against HIV (83). Berberine (Figure 2) is a benzylisoquinoline alkaloid found in plants such as *Berberis* spp. and potentially effective against trypanosomes and plasmodia (84).

Conclusions

At the end of this survey, it seems that some pediatric infections may be successfully managed with non-conventional phytotherapeutics. Not least, pediatric patients may also benefit from adjuvant therapy, *i.e.,* combined treatment with herbal remedies and conventional therapies, to improve the efficacy of conventional drugs, decrease their adverse effects at the cell-tissue-organ-organism level and reduce the occurrence of microbial strains resistant to antibiotics. We exposed the effect of a treatment based on one plant, such as *P. sidoides* root and *V. odorata* flower, or an herbal formula such as Ding-Chuan-Tang, Mai-Men-Dong-Tang, and Mao-to, on pediatric disorders. The synergy of the phytochemical compounds found in these plant, phenols, flavonoids, coumarins, quinones, tannins, terpenes, and alkaloids, is responsible for the beneficial effects of the treatments. In this view, traditional healing systems represented and still represent an unlimited source of active ingredients to be tested in terms of preclinical (*in vitro/in vivo*) assays, in human/in pediatric patient efficacy and safety.

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Conflicts of interest

The authors declare no conflict of interest.

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