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Editorial

# Integrative approaches to antimicrobial resistance

Antimicrobial resistance (AMR) is a serious public health issue which leads to increased time spent in hospital, increased mortality and has associated economic costs. Effective antimicrobial medicines are essential for conducting surgical procedures and many other health care practices. Many of these antimicrobial medicines are also used in livestock farming and for many non-life threatening conditions, thereby increasing exposure of bacteria to antibiotics increasing the chances for the development of antimicrobial resistance over time. In human healthcare, many people use antibiotics to treat viral infections or other conditions which would naturally resolve over time, which also increases the development of AMR.

The WHO and other organisations are developing action plans to counter the growing antimicrobial resistance problem [1]. They have called for a One Health approach which involves stakeholders from all sectors and disciplines since AMR will affect everyone regardless of health condition. Interestingly, many whole medical systems, for instance anthroposophic medicine, traditional Chinese medicine and Ayurveda have developed clinical practices that make use of far less antibiotics than modern medicine [2]. Furthermore, there is evidence that general practitioners additionally trained in integrative medicine practices prescribe fewer antibiotics [3]. However, it appears that the chances offered by integrative medicine practices have not yet been considered by the WHO global action plan.

There is great potential for discovering strategies to counter AMR in the field of integrative medicine. These strategies need to be further implemented in regular health care systems and at the same time the effects of those implemented strategies need to be evaluated in terms of efficacy, safety, cost effectiveness, and patient experience. This special issue on 'Integrative approaches to antimicrobial resistance' brings together a varied palette of new research papers that illustrate how the field is developing and offers promising possibilities for the further development of integrative medicine practices to counter AMR.

The urgency of antimicrobial resistance is specifically addressed in two opinion papers in the Special issue. Hu et al. describe the increasing awareness of the UK government about the AMR problem. According to the former UK Chief Medical Officer Professor Dame Sally Davies "antimicrobial resistance poses a catastrophic threat". The UK government made AMR a priority, announced in their disease strategy 2020–2025 that the UK will become a world player in countering AMR, and allocated 32 million pounds for research in 2018 (Hu et al. https://doi.org/10.1016/j.eujim.2020.101136). Young and Craig (https://doi.org/10.1016/j.eujim.2020.101072) discuss the urgency of antimicrobial resistant tuberculosis, which accounts for a third of deaths due to AMR and is the only antimicrobial resistant pathogen infectious through inhalation known so far. The authors discuss preliminary research about the possibilities of a Japanese traditional moxibustion treatment especially for people with latent tuberculosis.

Of course COVID-19 is the most recent epidemic rapidly spreading around the world with disastrous consequences for many people. In China there is rapidly growing body of experience and research about the use of traditional medicine alongside conventional treatment to treat COVID-19. This special issue contains a paper by Ho et al. (https://doi.org/10.1016/j.eujim.2020.101116) describing the official China National Guidelines for treating COVID-19 with Traditional Chinese Medicine. Zhang et al. (https://doi.org/10.1016/j.eujim.2019.101045) describe in their paper the quality assessment of clinical practice guidelines for the use of Chinese and Western medicine for acute bronchitis. This paper shows that the quality of guidelines concerning Chinese medicines is still insufficient and provides recommendations for improvement. These papers are examples of what is needed to employ traditional medicine in a standardized manner to treat known or unknown infectious diseases and thereby contribute to a reduction of AMR.

Most of the research papers in this special issue deal with discovering antimicrobial, antioxidant, antiviral or toxicological features of plant extracts that are traditionally used in various parts of the world. One of those studies is an RCT on the effects of *Hypericum perforatum* oil on the healing process after episiotomy. Women using the oil reported significantly less perineal pain and faster wound healing than women in the control group (Cobanoglu & Sendir https://doi.org/10.1016/j.eujim.2019.100995). Beside this RCT there are 24 in vitro studies with plant extracts measuring antimicrobial activity, and several studies antioxidant activity and cytotoxicity as well. Six of those 23 studies make use of antimicrobial resistant bacterial strains (Chacon et al. https://doi.org/10.1016/j.eujim.2019.100996, Liu et al. https://doi.org/10.1016/j.eujim.2019.100999, Imane et al. https://doi.org/10.1016/j.eujim.2020.101074, Yamada et al. https://doi.org/10.1016/j.eujim.2019.101016, Aygul & Serbetci https://doi.org/10.1016/j.eujim.2020.101061, Saki et al. https://doi.org/10.1016/j.eujim.2020.101146) and one study looked at antiviral activity (Angamuthu et al. https://doi.org/10.1016/j.eujim.2019.04.008). In four of the studies isolated compounds are used instead of plant extracts with a mixture of compounds (Sunita & Palaniswamy https://doi.org/10.1016/j.eujim.2019.101025, Nirmal et al. https://doi.org/10.1016/j.eujim.2020.101072, Shaikh et al. https://doi.org/10.1016/j.eujim.2019.100983, Alagesan et al. https://doi.org/10.1016/j.eujim.2019.100984).

Abuja et al. (https://doi.org/10.1016/j.eujim.2019.101010) shows antimicrobial activity of ethyl acetate *Murraya hoenigii* leaf extracts against 9 bacterial strains. *Murraya hoenigii* is a small spreading shrub growing in India and Malaysian which is traditionally used as blood purifier, depressant and to counter inflammation. Sharma et al. (https://doi.org/10.1016/j.eujim.2019.101000) reports on *Goniothalamus wynaadensis* Bedd., a medicinal plant used by several tribes in India to treat joint related ailments. Ethyl acetate and water

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extracts of the leaves both show antimicrobial activity against gram positive and negative bacteria and cytotoxic activity against cancer cell lines. *Cercis siliquatrum* L. (Judas tree) flowers are used in Turkey as an antiseptic (Amer et al. https://doi.org/10.1016/j.eujim.2019.05.007) report antimicrobial activity of the common US weed *Persicaria pensylvanica* flower, leaf, stem and root extracts against *Staphylococcus aureus*. Sajout et al. (https://doi.org/10.1016/j.eujim.2019.101017) studied the antimicrobial effects of a dichloromethane extract of *Lavandula tenuisecta*, a lavendula species common in Morocco. One paper by Sun et al. (https://doi.org/10.1016/j.eujim.2020.101115) reports higher antimicrobial effects of Chinese licorice granules (*Glycyrrhiza uralensis*) compared with water extracts of the licorice against 4 bacterial strains. Chinese licorice is widely used in veterinary to treat animals with bacterial infections. Al-lahham et al. (https://doi.org/10.1016/j.eujim.2019.101039) report on the antioxidant, anticancer and antimicrobial activities of hexane, acetone and methanol extracts of *Nicotiana tabacum* L. root against 5 bacterial strains. Ethanol and water extracts of *Capparis brevispina* DC shows antimicrobial activities against gram-negative bacteria and some fungi (Subramanian et al. https://doi.org/10.1016/j.eujim.2019.101038). Jaradat et al. (https://doi.org/10.1016/j.eujim.2020.101066) report varying antimicrobial, antilipase, antioxidant and anti-amylase activity of methanol, water, acetone and hexane extracts of *Anchusa ovata* Lehm. Zegeye et al. (https://doi.org/10.1016/j.eujim.2020.101121) studied the antimicrobial activity of *Lavandula anguistifolia*, *Cimpopogon citrus*, *Mentha piperita* against *S. aureus*, *E. coli* and *C. albicans*. Salim et al. (https://doi.org/10.1016/j.eujim.2019.100955) report cytotoxic activity of Malaysian honey, *Trigona itama*.

Two studies focussed on screening large numbers of plant extracts. The most common medicinal plants traditionally used to treat stomach pains and digestive disorders in Cameroon were identified and collected by Ngnameko et al. (https://doi.org/10.1016/j.eujim.2019.100957). All plant extracts demonstrated anti-*Helicobacter pylori* activity, of which seventeen plant extracts also demonstrated a reduction of *Helicobacter pylori* adhesion to mouse stomach tissue. In line with this work a survey was conducted resulting in the identification of 71 medicinal plants used in Uganda to boost the immune system of people living with HIV/AIDS (Anywar et al. https://doi.org/10.1016/j.eujim.2019.101011). Alva et al. (https://doi.org/10.1016/j.eujim.2019.100931) tested quorum sensing activity of 65 Mangaluru region, Indian vegetables and spices against *Pseudomonas aeruginosa*, and found activity in *Cinnamomum verum* leaf, *Solanum melongena* fruit, and *Syzygium aromaticum* leaf.

The above papers indicate that substantial effort is put into discovering more natural and sustainable methods to counter bacterial infections. This approach is also important for the discovery of natural anti-viral agents. One paper by Angamuthu et al. in this special issue addresses the anti-viral effects of plant extracts. The effect of *Punica granatum* L., *Momordica charantia* L., *Andrographis paniculata* Nees. and *Melia azedarach* L. leaves against human Herpesvirus-3 were studied, discovering comparable anti-viral activity of aqueous extract of *Punica granatum* L. leaves to acyclovir.

In four studies the antimicrobial potential of isolated compounds from plants are discussed. Sunita & Palaniswamy (https://doi.org/10.1016/j.eujim.2019.101025) used *Aegle marmelos* fruit pulp to synthesise silver nanoparticles which were suspended in a gel. Antimicrobial activity of this gel was found against 6 bacterial strains. In Shaikh et al. (https://doi.org/10.1016/j.eujim.2019.100983) several diterpenoids from *Andrographis paniculata* Burm. F. were found to have promising cyclooxygenase inhibiting, antioxidant and anti-proliferative activity. Alagesan et al. (https://doi.org/10.1016/j.eujim.2019.100984) found significant antioxidant, antimicrobial and antiproliferative activities of 5,7-dihydroxy-4-phenyl-2H-chromen-2-one, a compound isolated from the medicinal plant *Ipomoea pes-caprea*. Nirmal et al. (https://doi.org/10.1016/j.eujim.2020.101072) screened the medicinal plants *Lantana camara* L., *Euphorbia hirta* L., *Mukia maderaspatana* L. M. Roem, and *Abutilon indicum* L. for compounds with anti-tuberculosis activity against multiple antibiotics resistant strains.

Six of the in-vitro studies used antimicrobial resistant strains to test their extracts. Chacon & Martino (https://doi.org/10.1016/j.eujim.2019.100996) studied the antimicrobial effects of *Aloe barbadensis*Miller against bacteria involved in bovine mastitis, one of the infectious diseases with the largest impact for the dairy industry. Aloe vera delayed the appearance of resistance in *Staphylococcus aureus* strains and adding Aloe vera to antibiotics allowed for a reduced antibiotics dose. Aygul & Serbetci (https://doi.org/10.1016/j.eujim.2020.101061) report antimicrobial effects of especially the ethanol extracts of *Hypericum lydium* against antimicrobial resistant *Staphylococcus aureus* isolates. Modified Ginkgo san extracts mixed with levofloxacin show a synergistic effect against the quinolone-resistant *Staphylococcus aureus* strain, but antagonistic effects against *Escherichia coli* (Yamada et al. https://doi.org/10.1016/j.eujim.2019.101016). In a paper by Liu et al. (https://doi.org/10.1016/j.eujim.2019.100999) synergistic effects are reported for the Chinese medicinal plant *Pithecellobium clypearia* against multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. In another study by Imane et al. (https://doi.org/10.1016/j.eujim.2020.101074) essential oils from *Rosmarinus officinalis* L., *Zingiber officinale* Roscoe., *Melaleuca alternifolia* Cheel., *Chymbopogon winterianus*, *Salvia sclarea* L. and *Syzygium aromaticum* show antibacterial effects against novel bacterial strains isolated from Moroccan patients and that none of these strains was resistant to any of the oils. Saki et al. (https://doi.org/10.1016/j.eujim.2020.101146) report on antibacterial properties of cinnamon, a spice used extensively in many traditional healing systems. *Cinnamomum zeylanicum* bark essential oil was found to have antibacterial effects against extensive drug resistant clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VR E. faecium), *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Escherichia coli*.

This special issue furthermore contains five systems biology papers. Systems biology is especially suitable for studying herbal medicines which contain multiple active components working in synergy and also working in various sites in the body to generate a healing response in the body. Systems biology is based on systems thinking, applying methods derived from complexity sciences such as network analysis, and aims to study relationships between variables in the context of the organism [4]. Zhang et al. (https://doi.org/10.1016/j.eujim.2019.101003) report on the search for target genes based on the active compounds in *Hedysarum multijugum* maxim. and *Angelica sinensis* radix to uncover the mechanisms of the effect of Qi invigorating and blood circulation promoting traditional Chinese medicines to treat pulmonary fibrosis. In this network pharmacology study gene targets were found indicating virus inhibition, inflammatory factor secretion, inhibition of oxidative stress, and apoptosis regulation. Another network pharmacology study reveals eight potential targets (TNF, IL-6, IL-1β, IL-2, JUN, MAPK1.MAPK8, EGFR) of the Chinese drug Jiu Wei Zhu Huang San against respiratory tract infections (Guo et al. https://doi.org/10.1016/j.eujim.2019.101013). Zou et al. (https://doi.org/10.1016/j.eujim.2020.101071) reports on the mechanisms of the classical Chinese formula Zhisousan used to treat chronic cough. The main targets that resulted from the network pharmacology analysis were IL-6, vascular endothelial growth factor A, epidermal growth factor receptor and caspase-3. Jia et al. (https://doi.org/10.1016/j.eujim.2020.101111) report on the use of Reduning injection a TCM with *Artemisiae annuae* herba, *Lonicerae japonicae* flos, and *Gardeniae* fructus to treat viral infections. A network pharmacology study revealed 8 key targets of the medicine, and support the hypothesis that the injection can inhibit viral-cell fusion, may have an effect on cytokine storms and protect patients from lung damage. In another network pharmacology study by Zhuang et al. (https://doi.org/10.1016/j.eujim.2020.101139) bioactive compounds and their target genes were studied to elucidate the pharmacological mechanisms of the traditional Chinese medicine Shanhuanglian for respiratory tract infections. Five active compounds

(quercetin, luteolin, baicalein, kaempferol, and wogonin) were found to play a central role in the anti-bacterial and anti-viral activity of the drug and three KEGG pathways were mainly involved.

Herbal medicines can play a major role in developing sustainable integrative practices using local herbs to boost the immune system and reduce the effects of inflammatory diseases. However, many herbal medicines are never tested in randomized controlled trials due to lack of financial resources. Baars et al. therefore argue for the use of expert knowledge to provide a lower level of evidence for using IM methods to treat infectious diseases. The authors show that 2 of the 9 most prescribed anthroposophic treatments (Hustenelixer and Echinacea) and 3 of 10 most prescribed homeopathic treatments (Belladonna, Hepar sulphuris, Mercurius solubilis) used for cough and sour throat have been studies in clinical trials (Baars et al. https://doi.org/10.1016/j.eujim.2020.101194).

Beside the development of novel antimicrobial products there is a need to increase awareness about health promotion, and appropriate use of antibiotics when necessary. Hammour et al. (https://doi.org/10.1016/j.eujim.2019.05.003) conducted a survey amongst 467 parents of young children in Dubai about use of antibiotics in the case of upper respiratory tract infections which are mainly caused by viral infections. 34 % of the parents believed that children with fever should be given antibiotics regardless of the cause, even though 49 % knew that URTIs were caused by a virus. Many parents administered antibiotics without medical advice.

One paper by Vagedes et al. (https://doi.org/10.1016/j.eujim.2020.101068) illustrates how an integrative medicine clinic in which children receive Anthroposophic medicine together with conventional medicine can reduce antibiotics use in children hospitalized for pneumonia. In 32 % of the 252 pneumonia episodes antibiotics were prescribed while in the literature 88–98 % antibiotics prescription is reported. Delayed prescription of antibiotics was needed in only 13 % of the patients with presumed bacterial pneumonia. This paper is a great example for other clinics struggling with antibiotics resistance and offers ideas for designing future strategies of reduced antibiotics use.

This special issue shows the enormous potential of herbal medicines in contributing to the development of sustainable, local, integrative medicine practices focussing on strengthening the immune system in order to deal with infectious diseases. This issue also shows that herbal medicines contain many active components that often work in synergy and on multiple targets in the human body. A shift in thinking from disease management towards health promotion is needed both in health care as well as in the general public in order to reduce antibiotics use and subsequently the development of antibiotic resistance.

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