*Expert Reviews in Molecular Medicine*

**cambridge.org/erm**

## Invited Review

*These authors contributed equally to this work.

**Cite this article:** Wang J, Wong Y-K, Liao F (2018). What has traditional Chinese medicine delivered for modern medicine? *Expert Reviews in Molecular Medicine* **20**, e4, 1–9. https://doi.org/10.1017/erm.2018.3

Received: 9 November 2017
Revised: 23 March 2018
Accepted: 27 March 2018

**Key words:**
Arsenic trioxide; Artemisinin; berberine; Danshen; mechanism of action; modern medicine; traditional Chinese medicine

**Corresponding author:** Jigang Wang and Fulong Liao, E-mail: wangjigang@u.nus.edu and fulong_liao@126.com



CAMBRIDGE UNIVERSITY PRESS

# What has traditional Chinese medicine delivered for modern medicine?

Jigang Wang[1,2,3,*], Yin-Kwan Wong[4,*] and Fulong Liao[1,2]

[1]Artemisinin Research Center, China Academy of Chinese Medical Sciences, Beijing 100700, China; [2]Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, 100700, China; [3]Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117600, Singapore and [4]Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore

The field of Traditional Chinese Medicine (TCM) represents a vast and largely untapped resource for modern medicine. Exemplified by the success of the antimalarial artemisinin, the recent years have seen a rapid increase in the understanding and application of TCM-derived herbs and formulations for evidence-based therapy. In this review, we summarise and discuss the developmental history, clinical background and molecular basis of an action for several representative TCM-derived medicines, including artemisinin, arsenic trioxide, berberine and *Salvia miltiorrhiza* or Danshen. Through this, we highlight important examples of how TCM-derived medicines have already contributed to modern medicine, and discuss potential avenues for further research.

## Introduction

Traditional Chinese Medicine (TCM) refers to the holistic approach to diagnosis, pathophysiology and therapy in the Chinese *materia medica*, based on over 2000 years of accumulated knowledge and practice (Ref. 1). Major aspects of the practice include herbal medication, acupuncture and other physical therapy such as massage (Refs 2, 3, 4). Outside of China, the practice is generally regarded as a complementary or 'alternative' form of medicine, although the international prevalence of the practice has been steadily increasing (Ref. 5). Acceptance of TCM by the scientific community has been limited at best. Certain guiding principles of TCM such as the concept of 'vital energy' are esoteric and difficult to validate under modern scientific methods, and the TCM approach to both diagnosis and treatment also fundamentally differs from conventional Western methods (Refs 6, 7). Nevertheless, there are select aspects of the practice that hold clear promise for modern evidence-based medicine. The field of Chinese herbals, in particular, has drawn increasing interest as a source of novel drugs and drug leads, which is unsurprising considering that many modern drugs are in fact derivatives of herbal medicines and natural products (Refs 8, 9, 10, 11). The awarding of part of the 2015 Nobel Prize in Physiology or Medicine for Tu Youyou's discovery and development of artemisinin, a potent antimalarial derived from the herbal *Artemisia annua*, is a clear example and reminder of the potential held by herbal medicine (Ref. 12). Looking ahead, further understanding and appreciation of the current status and successes of TCM herbals will be important for continued developments in the field. In this paper, we seek to provide an overview of some of the major contributions that Chinese herbals have made to modern medicine, focusing on the background and process of discovery, molecular mechanisms, clinical evidence for established treatments as well as novel and promising treatments under development.

## Artemisinin in the treatment of malaria

Malaria is caused by the *Plasmodium* genus of endoparasites and remains a global health concern with 212 million new cases and 429 000 deaths as recently as 2015 (Ref. 13). The artemisinin family of sesquiterpene lactone compounds, including artemisinin itself as well as synthetic derivatives such as dihydroartemisinin, artesunate and artemether (Fig. 1), currently serve as the standard treatment and represent the front line of antimalarial drugs with remarkable potency, specificity and safety (Refs 14, 15, 16). ACT (artemisinin-based combination therapies) remain the most effective and recommended treatment regimens for uncomplicated malaria, especially in cases caused by the prevalent *Plasmodium falciparum* strain of parasites (Refs 17, 18). The compound is derived from *A. annua* or 'sweet wormwood', which has been used in TCM (where it is known as 'Qinghao') for the relief of periodic fevers, a symptom of malaria (Ref. 19). The earliest documentation of such usage dates back to the East Jin Dynasty between 317 and 420 A.D., in Ge Hong's *A Handbook of Prescriptions for Emergencies* (Refs 12, 20).

The story of artemisinin is likely the most well-known example of Chinese medicine's contributions to modern medicine, given its outstanding real-world results and the recognition of the 2015 Nobel Prize. Under the Chinese nationwide antimalarial research initiative 'Project 523', the antimalarial agency headed by Tu Youyou in her institute performed extensive

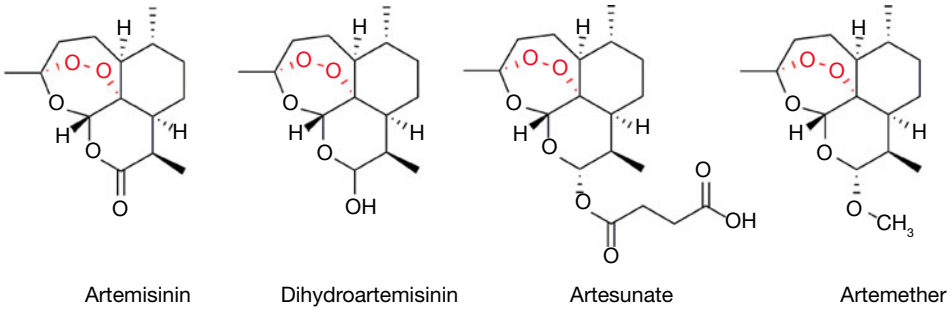



**Figure 1.** The structures of artemisinin and its clinically used derivatives.

screening without success in hundreds of Chinese medicine-derived compounds, including *A. annua* (Refs 12, 20). With reference to the ancient literature which described preparation conditions for the herb, Tu then attempted a low-temperature approach in extracting the active components of *A. annua* and in 1971 identified a particular non-toxic extract which displayed close to 100% efficacy in mouse malaria models. The extract was quickly brought to clinical trial where recovery and full parasite clearance was reported in over 90% of cases. The active compound of *A. annua* was then successfully purified by the same group in 1972 and named artemisinin, or Qinghaosu in Chinese Mandarin. Finally, the full stereochemical structure of artemisinin was elucidated and published in 1977 (Ref. 21). Further work by Tu and others in the modification and derivitisation of artemisinin set the foundation for further understanding of critical functional groups as well as the development of artemisinin derivatives such as dihydroartemisinin, artesunate and artemether, which now serve as indispensable antimalarials worldwide (Refs 22, 23).

Since artemisinin began to draw global attention in the early 1980s, numerous clinical studies have been performed in endemic regions to assess its safety and potency either in combination with other antimalarials or as a monotherapy. In particular, studies from China, Africa and Southeast Asia over the past three decades including recent meta-analytical data have convincingly demonstrated the outstanding clinical properties of artemisinin. Clinical results were marked by rapid parasite clearance and improvement of symptoms, especially for uncomplicated *P. falciparum* malaria in combination with longer-acting antimalarials such as mefloquine, lumefantrine, benflumetol and piperaquine (Refs 17, 18, 24, 25, 26, 27, 28, 29). Results in severe malaria have likewise been generally positive for artemisinin derivatives compared with other treatments such as quinine, albeit with reduced efficacy compared with uncomplicated cases (Refs 30, 31, 32). Reports of major adverse effects have been minimal, especially considering the volume of available data and the ubiquity of the drug (Refs 15, 33). In addition to its place as the most important antimalarial, limited clinical success has also been reported for the role of artemisinin in other diseases such as colorectal cancer, and research is ongoing for the re-purposing of artemisinin for various nonmalarial roles (Refs 34, 35, 36, 37, 38).

Despite the widespread usage of artemisinin, the current molecular understanding of its mechanism of action remains incomplete. The artemisinin compounds are sesquiterpene lactones sharing the 1,2,4-trioxane pharmacophore, which contains an endoperoxide bridge that is thought to be essential for its pharmacological activity against both malaria as well as cancer (Ref. 39). Artemisinin itself is a prodrug that must be activated via cleavage of this endoperoxide bridge for drug activity, although the mechanism of this activation remains an issue of some debate (Ref. 40). Both free ferrous iron ($Fe^{2+}$) as well as haem released from haemoglobin digestion have been proposed to activate artemisinin (Refs 41, 42, 43). Reductive ion transfer (from iron or haem) is proposed to induce homolytic cleavage of the endoperoxide bridge, producing oxygen-centred radicals that subsequently isomerise to form reactive carbon-centred radicals (Refs 44, 45, 46). In an alternative theory, free $Fe^{2+}$ functions as a Lewis acid in catalysing the heterolytic cleavage of the endoperoxide, generating cationic intermediates and hydroperoxides that can subsequently generate reactive hydroxyl radicals (Ref. 47). While free ferrous iron has been understood to be responsible for artemisinin activation, recent evidence from mass spectrometry and proteomics approaches have demonstrated that redox active haem could also play an important and possibly principal role in the process (Refs 42, 43, 48, 49). It will be important to clearly elucidate the activation mechanism of artemisinin as this could directly relate to its remarkable specificity.

Following activation, the downstream mechanisms by which artemisinin achieves its antimalarial properties are likewise incompletely understood (Ref. 40). Malaria parasites break down host cell haemoglobins, releasing large amounts of haem in the process (Refs 50, 51). Haem build-up then leads to haematin formation which can induce oxidative and lytic damage to the parasite (Ref. 52). As a defence mechanism, the parasites are able to crystallise toxic haematin to the nontoxic haemozoin (Ref. 53). Activated artemisinin has been shown to be able to bind and alkylate haem both in vitro and in vivo, possibly preventing haemozoin formation and causing a toxic accumulation of haem (Refs 54, 55, 56, 57). Likewise, activated artemisinin is also known to be able to alkylate protein targets, which could interfere with critical biological functions and contribute to toxicity (Refs 58, 59). The identification of such protein targets of artemisinin has been a topic of great interest, and well-described examples include TCTP (translationally controlled tumour protein) and PfATP6 (Refs 60, 61). In particular, PfATP6 (a sarco/endoplasmic reticulum $Ca^{2+}$-ATPase or SERCA) was reported to be bound and inhibited by artemisinin, making it a putative target of interest (Ref. 62). Recent reports using mass spectrometry-based proteomics approaches have highlighted a potentially promiscuous and indiscriminate targeting mechanism of artemisinin, where cellular targets including proteins are nonselectively alkylated in a proximity-dependent manner (Refs 42, 43, 63). Our 2015 study identified over 100 binding targets of artemisinin using chemical probes (Fig. 2), implicating multiple cellular functions, including biosynthetic and metabolic pathways (Ref. 42). Under such a model, a large number of proteins may be affected simultaneously and many critical biological pathways could be disrupted. The specificity of artemisinin, in this case, could then be largely attributed to the conditions and the extent of drug activation, rather than the specific targeting of protein effectors (Fig. 3). A combination of haem- and protein alkylation by artemisinin (which is specifically activated in high-haem, high-iron parasite conditions) could possibly explain both the specificity and potency of the drug. Nevertheless, it should be considered that certain proteins or other cellular targets could play a

https://doi.org/10.1017/erm.2018.3 Published online by Cambridge University Press

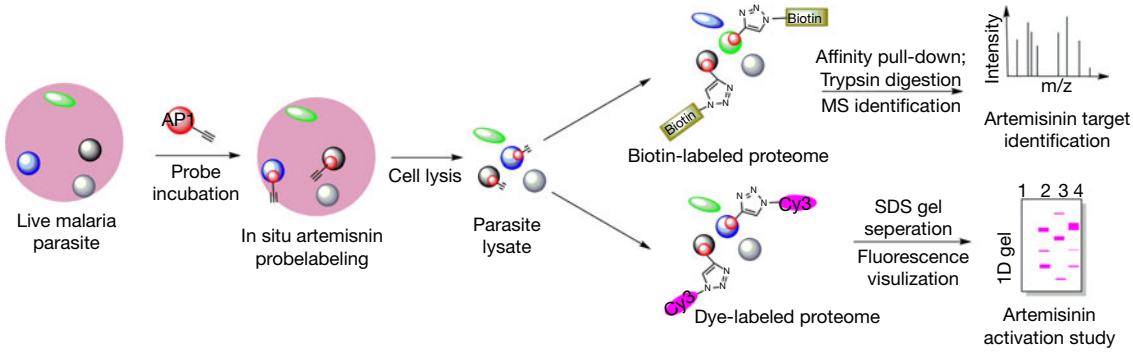



**Figure 2.** General workflow of a chemical biology approach to study the targets and activation of artemisinin using artemisinin-based chemical probes.

disproportionately large role in the downstream effects of artemisinin. The elucidation of such targets remains a challenge for further understanding and development of this important drug. Ultimately, the story of artemisinin's discovery and development is a classic example of the value held in traditional medicine and traditional literature. Considering the long history of TCM as well as other systems of traditional medicine, it would surely not be surprising that other hidden gems already described and used by our predecessors yet remain to be discovered.

## Arsenic trioxide in the treatment of acute promyelocytic leukaemia

Arsenic compounds, though well known for their toxicity, have been used for therapeutic purposes for possibly thousands of years. In accordance with the TCM principle of 'attacking poison with poison', the toxic compound arsenic trioxide (ATO, $As_2O_3$) or 'Pi Shuang' has been used both topically and orally in TCM as a medication for fevers, skin conditions and many other diseases (Ref. 64). In TCM as well as pre-modern Western medicine, ATO has also been used in the treatment of cancer, including leukaemia, and ATO was, in fact, a common treatment for chronic myeloid leukaemia in the early 20th century (Ref. 65). With the advent of more sophisticated cancer therapeutics including chemotherapy and the concerns of toxicity, however, the therapeutic use of ATO outside of China was eventually largely phased out (Ref. 66).

In 1996 and 1997, clinical and in vitro data from China reported by Shen et al. and Chen et al. were published in *Blood* detailing the application of ATO to the treatment of acute promyelocytic leukaemia (APL), drawing international attention to the compound which has already been in development in China for over a decade (Refs 67, 68, 69). The efforts could be traced to the work of Dr Zhang Tingdong and colleagues at Harbin Medical University during the 1970s, who studied the first TCM-derived formulation of ATO in the treatment of

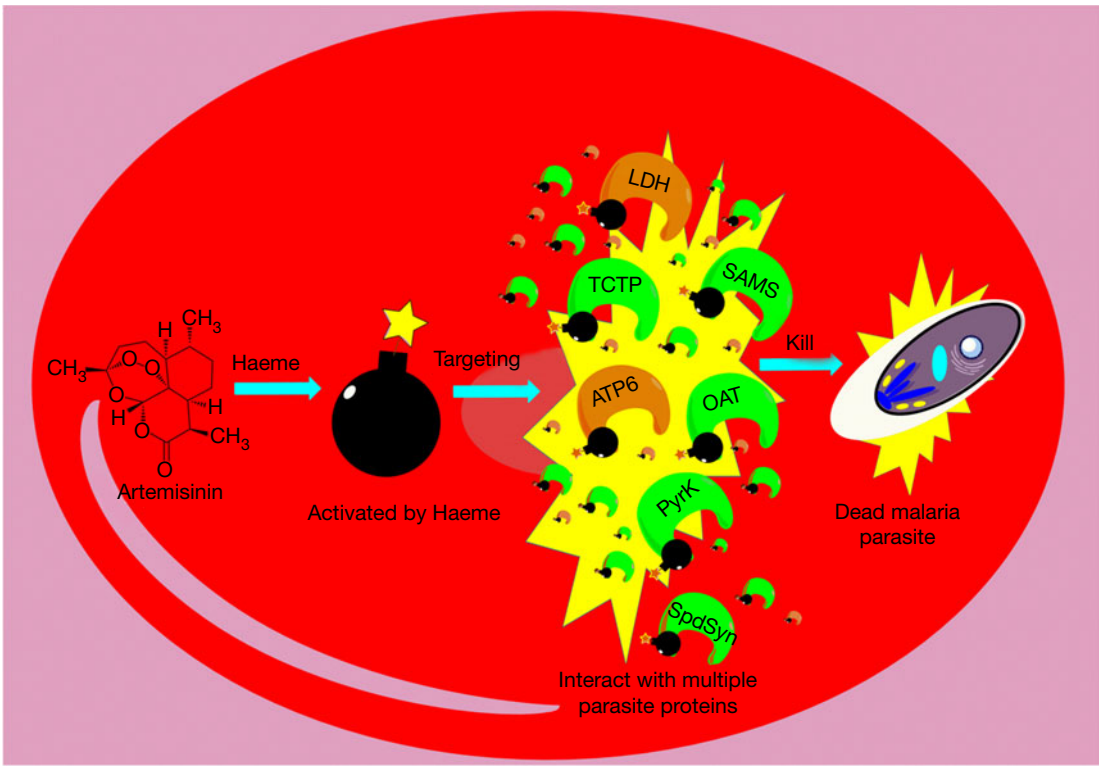



**Figure 3.** The proposed mechanism of action of artemisinin for its anti-malaria effects. Artemisinin is activated by haem which is released during haemoglobin digestion by the malaria parasite. This generates reactive radicals which alkylate a range of parasite proteins, eventually killing the parasite. $Ca^{2+}$-ATPase (ATP6), the translationally controlled tumour protein (TCTP), ornithine aminotransferase (OAT), pyruvate kinase (PyrK), L-lactate dehydrogenase (LDH), spermidine synthase (SpdSyn) and S-adenosylmethionine synthetase (SAMS).

https://doi.org/10.1017/erm.2018.3 Published online by Cambridge University Press

leukaemia and identified ATO as the principal active component (Ref. 70). APL itself was an acute and aggressive form of leukaemia that saw considerable improvement in treatment outcomes following the development of all-trans retinoic acid (ATRA) therapy, which was also developed and reported in the late 1980s by Chinese researchers (Refs 71, 72). However, ATRA treatment alone suffered from a high rate of relapse, necessitating novel and complementary therapeutic approaches (Ref. 73). The development of ATO for APL treatment by Zhang and others continued in China with promising clinical results, and the 1997 publications were followed up by Soignet et al. in their 1998 clinical report (Ref. 74). Much like artemisinin, the outstanding clinical properties of ATO led to rapid adoption and development by the international community. ATO in combination with ATRA therapy is currently a standard APL treatment, and the clinical success of the treatment in both newly diagnosed and relapsed cases has been well demonstrated and comprehensively reviewed in several authoritative works (Refs 75, 76, 77, 78, 79, 80, 81).

The core mechanisms of ATO in APL treatment are currently understood to be a concentration-dependent dual effect by the induction of cancer cell differentiation and apoptosis. In initial in vitro testing on APL NB4 cell lines, Chen et al. reported robust apoptosis induction by ATO at higher concentrations between 0.5–2 μM and partial differentiation at lower (0.1–0.25 μM) over longer time periods up to 10 days (Ref. 67). ATO-induced apoptosis is mediated by the canonical mitochondrial pathway, inducing mitochondrial membrane potential collapse by targeting mitochondrial membrane proteins and demonstrating characteristic cytochrome *c* release, caspase 8 activation and cleavage of poly (ADP-ribose) polymerase (PARP) (Refs 82, 83, 84, 85, 86). Notably, ATO-induced apoptosis is associated with downregulated Bcl-2 expression and can be inhibited by Bcl-2 overexpression (Refs 67, 83). Cellular redox conditions have also been shown to be important for ATO-induced apoptosis, possibly by interfering with the ability of ATO to bind protein effectors through interactions with exposed sulfhydryl (–SH) groups of cysteine residues (Refs 66, 87). Accordingly, modulation of the antioxidant glutathione (GSH) system has been reported to affect cancer cell sensitivity to ATO (Ref. 88). Other reported mechanisms of ATO-induced apoptosis include ROS production and oxidative damage through the modulation of ROS-related genes, inhibition of NF-κB through the binding of IκB kinase (IKK), and further effects on many other signalling pathways, including MAPK, JAK-STAT and JNK which have been extensively reviewed elsewhere (Refs 81, 87, 89, 90).

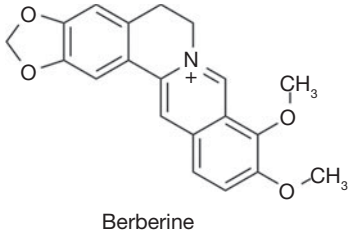
The mechanisms by which ATO induces differentiation are less well understood but are likely related to its interactions with the PML–RARα fusion protein which is characteristic of the vast majority of APL cases. This oncoprotein is caused by a particular t(15;17) chromosomal translocation which results in a fusion of the retinoic acid receptor alpha (RARα) gene and promyelocytic leukaemia (PML) gene (Refs 91, 92). Endogenous PML is a tumour suppressor that localises to the nucleus and forms distinct macromolecular structures known as PML nuclear bodies (PML-NB) which are involved in transcriptional regulation (Refs 93, 94). Functional PML-NB prevents the development of malignancy and is required for terminal differentiation. In the case of APL, expression of the PML-RARα fusion protein disrupts the normal PML-NB structure, resulting in errant protein-protein interactions, failure of differentiation and eventual leukemogenesis (Ref. 72). Through the induction of ROS formation and direct interaction with PML–RARα, ATO is reported to restore endogenous PML-NB structure and function through the induction of PML–RARα multimerisation, SUMOylation and eventual proteasomal degradation (Refs 95, 96, 97, 98). This ability of ATO to target a key oncogenic protein (as a so-called oncogene-directed therapy) underlies its remarkable specificity and efficacy. In this regard, the mechanism appears to be related to ATRA therapy (and hence the RAR pathway) which also induces differentiation and PML–RARα degradation, although ATO and ATRA are known to interact with different regions of the fusion protein (Refs 95, 99). This distinction could partly explain the synergism between ATO and ATRA in combination, as well as the effectiveness of ATO in ATRA-resistant and relapsed cases (Ref. 87). In addition to the restoration of PML-NB function and extensive effects on gene regulation and cancer cell stemness, other factors such as miRNA have also recently been reported to contribute to ATO-induced differentiation (Refs 100, 101).

Beyond ATO, the general study of TCM-derived natural products and compound formulations for cancer therapy is an area of immense interest both within and outside China. Apart from the ongoing discovery and characterisation of active antineoplastics, the use of TCM as an effective adjuvant therapy in combination with conventional treatments as well as the role of TCM in pain management and palliative care should also not be overlooked (Refs 102, 103, 104, 105, 106, 107). For instance, the four-herb formulation PHY906 currently undergoing multiple clinical trials has been identified as an effective modulator of chemotherapy toxicity for multiple chemotherapy treatments (Refs 108, 109, 110). Given the recent resurgence of interest in natural products and the success of artemisinin and ATO in their respective roles, it is not difficult to imagine that more drugs and treatments of great potential remain within the TCM *materia medica* (Ref. 9). It will be of great interest moving forward to observe the potential contributions of TCM to evidence-based cancer therapy.

## Berberine in the treatment of type 2 diabetes mellitus

The use of TCM for the prevention and treatment of diabetes in China dates back over 2000 years where diabetic symptoms were known as 'Xiaoke', or increased thirst (Ref. 111). Many herbs and formulations have been developed and remain widely in use in China for TCM treatment of type 2 diabetes mellitus in the present day (Ref. 112). Among those treatments, the isoquinone alkaloid known as berberine (Fig. 4) has stood out for its clinically demonstrated hypoglycemic and hypolipidemic properties. Berberine is an active component of *Coptis chinensis* rhizomes, a Chinese herbal used for the relief of diabetes as well as gastrointestinal disorders (Ref. 113). Traditionally known for a wide spectrum of antimicrobial activities, the application of berberine to diabetic symptoms was first reported and followed up in a Chinese study in the late 1980s, when berberine used in an antidiarrhoeal capacity for diabetic patients was shown to lower blood sugar (Refs 114, 115).

Compared with well-established treatments such as artemisinin or ATO, clinical study of berberine as an antidiabetic is at a relatively early stage with pilot trials based in China first being reported in 2008. In comparative studies between berberine and the first-line treatment metformin in 36 newly-diagnosed type 2 diabetics, Yin et al. reported comparable effects on the regulation



Berberine

**Figure 4.** The structure of berberine.

https://doi.org/10.1017/erm.2018.3 Published online by Cambridge University Press

of glucose metabolism with significant ($P < 0.01$) decreases in indicators such as haemoglobin A1c, fasting blood glucose and postprandial blood glucose. Berberine outperformed metformin in the regulation of lipid metabolism, effecting a decrease in plasma triglycerides and cholesterol over 13 weeks at a significant improvement over metformin ($P < 0.05$). In parallel, a study was conducted on the use of berberine in combination therapy with existing antidiabetic treatment for 48 patients with poorly controlled diabetes. The use of berberine significantly improved both glycemic and lipidemic parameters compared with baseline, and treatments were generally well tolerated with limited and transient adverse gastrointestinal reactions in the combination group but no functional liver or kidney damages (Ref. 116). In a double-blind randomised controlled trial in 110 patients published in the same year, Zhang et al. likewise reported the efficacy and safety of berberine in the treatment of newly diagnosed type 2 diabetics. Both glycaemic and lipidaemic indicators exhibited significant improvements compared to the placebo, and secondary outcomes including reduced body weight and blood pressure were also positive (Ref. 117).

As reviewed in meta-analyses published 2012 and 2015, subsequent randomised clinical trials (14 and 27 studies reviewed respectively) continued to provide positive results, with significant support for the efficacy of berberine in improving glycaemic control that is at least comparable or not inferior to current first-line treatments (Refs 118, 119). Considering that berberine is chemically distinct from other first-line options, the compound stands out as a potential novel antidiabetic both as monotherapy or in combination with other treatments for cases which respond poorly to existing treatments. Other plus points for berberine include a low cost of production, safety and a multi-faceted mechanism that appears to target multiple aspects of diabetes (Refs 119, 120). Berberine has been reported to target glucose metabolism through both insulin-dependent and independent pathways, increasing insulin sensitivity (partly through increased insulin receptor expression), insulin secretion, glucose uptake, and stimulating activation of the AMP-activated protein kinase (AMPK) pathway (Refs 121, 122, 123, 124). Other mechanisms including modulating liver metabolic function through regulation of gene expression, reduction of intestinal glucose uptake through the inhibition of $\alpha$-glucosidase, modulation of gut microbiota composition (through antimicrobial activity) and antioxidant properties have also been reported, among others (Refs 125, 126, 127, 128). In contrast, the antihyperlipidemic efficacy and mechanism of berberine are comparatively less understood and will require additional study. Importantly, the compound suffers from relatively poor bioavailability and novel formulations to improve its pharmacological profile will be of interest (Ref. 129). Further clinical and mechanistic studies, especially high-quality and unbiased clinical trials, will be crucial for the continued development of TCM-derived antidiabetic treatments such as berberine as well as other promising formulations (Refs 130, 131). In any case, the development of TCM for both the management and prevention of diabetes remains widespread and an ongoing subject of great research interest in China, and should be worthwhile of continued observation for contemporary applications.

## Salvia miltiorrhiza in the treatment of cardiovascular diseases

Cardiovascular and cerebrovascular diseases, especially ischemic heart disease and stroke, remain consistently among the leading causes of death worldwide. In China, the use of TCM medication and principles in treating such conditions is among the most developed fields in TCM practice and research. Generally termed 'huo xue hua yu' or 'activating blood circulation and removing blood stasis', this branch of TCM makes use of a wide range of herbs and formulations to achieve antithrombotic, antiplatelet aggregation, vasodilative and cardioprotective effects (Ref. 132). Among the many Chinese medicines used for such purposes, the root of the *S. miltiorrhiza* or 'Danshen' is particularly known in China as well as other parts of Asia for its historical and contemporary usage in the treatment of many cardiovascular and cerebrovascular diseases (Ref. 133). Remarkably, a complex formulation of Danshen, the Compound Danshen Dripping Pill, holds the distinction of being the first TCM-derived product that was approved in 1997 for phase II clinical trials by the US Food and Drug Administration (FDA) (Ref. 134). Phase II trials for the application of the product (trademarked 'Dantonic') for the prevention and treatment of stable angina were completed with positive results in 2010 (Ref. 134), and phase III trials were completed in 2016. The Compound Danshen Dripping Pill, Danshen products in other forms including Danshen-based drug injections have been the subject of extensive clinical and mechanical study in China. Positive clinical findings have been reported for the application of Danshen-based medication for ischaemic stroke, angina pectoris, intercranial haematoma and acute myocardial infarction, among others (Refs 135, 136, 137, 138). In particular, 16 out of 16 published meta-analyses on the use of Compound Danshen Dripping Pills for the management of coronary heart disease have reported positive findings on efficacy and safety, although additional high-quality and unbiased data remains necessary for further judgment (Ref. 138).

This recognition of Danshen and Danshen-derived formulations by the FDA is noteworthy due to an important distinction between Danshen and other previously recognised TCM-derived drugs. Unlike artemisinin, ATO or even berberine, which are clearly defined singular compounds purified from some herb, mineral or mixture, Danshen extracts and compound formulations contain multiple bioactive components with complex mechanisms of action which is characteristic of most medicinal herbs (Ref. 139). This property is conventionally considered undesirable in modern rational drug design, which values well-defined molecular targets and mechanisms for each drug. This represents a contrast in ideology compared to Chinese medicine, which instead focuses on a holistic approach based on the overall symptoms and presentation of each individual patient and uses complex mixtures of herbs and other forms of treatment (Ref. 6). Compared with previous examples of successful drugs developed from Chinese medicine, the fact that the complex formulation of Danshen-based medication appears to also be the most effective is perhaps indicative that the Chinese philosophy can also be valid, at least on occasion (Refs 140, 141).

To date, at least 50 components have been purified and identified from Danshen extracts, which can be largely categorised into hydrophilic compounds (including various polyphenolic acids) and lipophilic compounds (mostly from the tanshinone family of diterpenes) (Ref. 139). Several of these are relatively well-studied and believed to contribute significantly to the pharmacological effects of Danshen. The phenolic acids including Danshensu, rosmarinic acid, caffeic acid and the salvianolic acids A and B have been reported to exhibit antioxidant, anticoagulant, vasodilative and cardioprotective effects, in addition to other biological activities including antineoplastic and hepatoprotective effects (Refs 139, 142). In particular, Danshensu (salvianic acid A) and salvianolic acid B have both been proposed as major contributors to the vasodilative and anticoagulant effects of Danshen extracts, acting through the modulation of calcium influx and the immune response, among other mechanisms (Refs 143, 144, 145, 146). Among the lipophilic compounds, the tanshinones which are mostly unique to the *Salvia* family (represented by tanshinone I, tanshinone IIA and cryptotanshinone) are well-studied and have

https://doi.org/10.1017/erm.2018.3 Published online by Cambridge University Press

been shown to exhibit significant antibacterial, antiinflammatory and antioxidant properties in addition to cardioprotective effects (Ref. 139). Outside these comparatively well-understood compounds, other constituents of Danshen have also been reported to contribute to the overall pharmacological effects of Danshen through multiple mechanisms including calcium modulation and the Akt–eNOS pathway (Refs 147, 148, 149). The chemical and biological properties of the prominent constituents of Danshen-based medicines are comprehensively reviewed in other authoritative publications, including a recent comprehensive characterisation of Danshen-based injection by mass spectrometry (Refs 139, 141, 142, 150). Despite the volume of available research, much remains to be understood with regards to the less-understood constituents and the interactions between the various active components of Danshen. Nevertheless, it appears evident that a combination of many bioactive components is necessary for the full efficacy of Danshen and other such herbal formulations. Pending the results of current and further clinical study, TCM-derived treatments of cardiovascular disease exemplified by Danshen should continue to be an area of great interest.

## Conclusion

Evidence-based TCM and the integration of TCM principles and medication with modern science and medicine is an area of tremendous ongoing interest and effort. As an overview of the contributions of the entire TCM practice to modern medicine, we have attempted to select several representative treatments in various stages of development to illustrate the progress that has been made in each respective field. However, it is important to reiterate that this is only a tiny representation of the available data and the ongoing effort in TCM research extending to a wide range of diseases. Where possible, we have included references to comprehensive and authoritative reviews that cover the respective fields in great detail and rigor.

One of the means by which TCM contributes to world medical development is to provide effective monomer chemical drugs. TCM is characterised by individual adjustment of multiple components and multiple targets which enables the body to transform from an abnormal to normal state. More research in this respect is yet to be carried out. Moving ahead, it will be important not only to appreciate the existing successes and the potential of TCM for contributing to modern medicine but also to work towards better realising this potential. Given the widespread nature of TCM usage in China for all manners of diseases, it is unsurprising that clinical data are often available in large abundance. However, the quality of clinical studies in terms of study methodology and the elimination of bias have remained significant areas of concern for TCM clinical research (Ref. 151). High-quality clinical data in conformance with international standards such as the CONSORT and TREND statements are absolutely essential for the further development and acceptance of TCM, and the improvement of clinical data quality will be a critical step for TCM research looking forward. At the same time, the advancement of 'omics' and high-throughput investigative techniques such as proteomics and genomics have led to significant progress in drug target identification and the elucidation of drug mechanisms, which remain crucial to modern rational drug design (Refs 152, 153). Considering the complex, multi-component nature of most TCM herbal treatments, the application of such investigative techniques to more complex formulations should yield great insights not only to drug mechanisms but also to the understanding of TCM principles and philosophies with the potential to greatly contribute to modern medicine. While certain aspects of TCM may remain as fringe topics in the context of modern medicine, the examples covered in this review have hopefully served to illustrate the potential within TCM herbals and by extension the practice of TCM as well as traditional medicinal systems as a whole. It would be a mistake to completely discount the value of experience accumulated over thousands of years based on specific aspects of the practice. The continued application and integration of scientific principles and techniques with traditional medicine will surely continue to serve modern medicine well.

**Acknowledgements.** This work was supported, in whole or in part, by the projects of National Natural Science Foundation of China (grant numbers 81641002 and 81473548); Major National Science and Technology Program of China for Innovative Drug (grant no. 2017ZX09101002-00X-00X); and the Fundamental Research Funds for the Central public welfare research institutes (grant no. ZZ10-024).

**Competing interests.** The authors declare that they have no competing interests.

## References

1. **Xu Q *et al.*** (2013) The quest for modernisation of traditional Chinese medicine. *BMC Complementary and Alternative Medicine* **13**, 1.
2. **Chan K** (1995) Progress in traditional Chinese medicine. *Trends in Pharmacological Sciences* **16**, 182–187.
3. **KJ C and H X** (2003) The integration of traditional Chinese medicine and Western medicine. *European Review (Chichester, England)* **11**, 225–235.
4. **Tang J-L *et al.*** (2008) Traditional Chinese medicine. *Lancet* (*London, England*) **372**, 1938–1940.
5. **Chan E *et al.*** (2010) Interactions between traditional Chinese medicines and Western therapeutics. *Current Opinion in Drug Discovery & Development* **13**, 50–65.
6. **Jiang WY** (2005) Therapeutic wisdom in traditional Chinese medicine: a perspective from modern science., *Trends in Pharmacological Sciences* **26**, 558–563.
7. **Dong J** (2013) The relationship between traditional Chinese medicine and modern medicine. *Evidence-Based Complementary and Alternative Medicine* **2013**, 153148.
8. **Newman DJ and Cragg GM** (2012) Natural products as sources of new drugs over the 30 years from 1981 to 2010. *Journal of Natural Products* **75**, 311–335.
9. **Cragg GM and Newman DJ** (2013) Natural products: a continuing source of novel drug leads. *Biochimica et Biophysica Acta* **1830**, 3670–3695.
10. **Corson TW and Crews CM** (2007) Molecular understanding and modern application of traditional medicines: triumphs and trials. *Cell* **130**, 769–774.
11. **Li JW-H and Vederas JC** (2009) Drug discovery and natural products: end of an era or an endless frontier? *Science* **325**, 161–165.
12. **Tu Y** (2016) Artemisinin – a gift from traditional Chinese medicine to the world (Nobel Lecture). *Angewandte Chemie (International ed. in English)* **55**, 10210–10226.
13. **Geneva: World Health Organization (2016)** World Malaria Report 2016. In World Malaria Report 2016 pp. 2.
14. **Geneva: World Health Organization** (2015) *Guidelines for the Treatment of Malaria*, 3rd Edn. Geneva: World Health Organization, p. 32, 72.
15. **van Agtmael MA, Eggelte TA and van Boxtel CJ** (1999) Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication. *Trends in Pharmacological Sciences* **20**, 199–205.
16. **Hoshen M** (2004) Artesunate combinations for malaria. *Lancet* (*London, England*) **363**, 737.
17. **Looareesuwan S *et al.*** (1992) Randomised trial of artesunate and mefloquine alone and in sequence for acute uncomplicated falciparum malaria. *Lancet* (*London, England*) **339**, 821–824.
18. **Bich NN *et al.*** (1996) Efficacy and tolerance of artemisinin in short combination regimens for the treatment of uncomplicated falciparum malaria. *American Journal of Tropical Medicine and Hygiene* **55**, 438–443.
19. **Klayman DL** (1985) Qinghaosu (artemisinin): an antimalarial drug from China. *Science* **228**, 1049–1055.

https://doi.org/10.1017/erm.2018.3 Published online by Cambridge University Press

20. **Tu Y** (2011) The discovery of artemisinin (Qinghaosu) and gifts from Chinese medicine. *Nature Medicine* **17**, 1217–1220.
21. **Collaboration Research Group for Qinghaosu** (1977) A new sesquiterpene lactone—Qinghaosu [in Chinese]. *Kexue Tongbao* **3**, 142.
22. **Collaboration Research Group for Qinghaosu** (1982) Chemical studies on Qinghaosu. *Journal of Traditional Chinese Medicine* **2**, 3–8.
23. **Wang M-Y** (2016) Publication process involving the discovery of artemisinin (Qinghaosu) before 1985. *Asian Pacific Journal of Tropical Biomedicine* **6**, 461–467.
24. **Li GQ *et al.*** (1984) Randomised comparative study of mefloquine, Qinghaosu, and pyrimethamine-sulfadoxine in patients with falciparum malaria. *Lancet* (*London, England*) **2**, 1360–1361.
25. **Looareesuwan S *et al.*** (1997) Open randomized trial of oral artemether alone and a sequential combination with mefloquine for acute uncomplicated falciparum malaria. *American Journal of Tropical Medicine and Hygiene* **56**, 613–617.
26. **von Seidlein L *et al.*** (1997) Treatment of African children with uncomplicated falciparum malaria with a new antimalarial drug, CGP 56697. *Journal of Infectious Diseases* **176**, 1113–1116.
27. **von Seidlein L *et al.*** (1998) A randomized controlled trial of artemether/benflumetol, a new antimalarial and pyrimethamine/sulfadoxine in the treatment of uncomplicated falciparum malaria in African children. *American Journal of Tropical Medicine and Hygiene* **58**, 638–644.
28. **Doherty JF *et al.*** (1999) A randomized safety and tolerability trial of artesunate plus sulfadoxine--pyrimethamine versus sulfadoxine-pyrimethamine alone for the treatment of uncomplicated malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **93**, 543–546.
29. **WWARN Artemisinin based Combination Therapy (ACT) Africa Baseline Study Group** *et al.* (2015) Clinical determinants of early parasitological response to ACTs in African patients with uncomplicated falciparum malaria: a literature review and meta-analysis of individual patient data. BMC Medicine 13, 212.
30. **Dondorp AM *et al.*** (2010) Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* (*London, England*) **376**, 1647–1657.
31. **McIntosh HM and Olliaro P** (2000) Artemisinin derivatives for treating severe malaria. *Cochrane Database of Systematic Reviews* (2), CD000527. DOI: 10.1002/14651858.CD000527.
32. **Sinclair D *et al.*** (2012) Artesunate versus quinine for treating severe malaria. *Cochrane Database of Systematic Reviews* (6), CD005967. DOI: 10.1002/14651858.CD005967.pub4.
33. **Efferth T and Kaina B** (2010) Toxicity of the antimalarial artemisinin and its dervatives. *Critical Reviews in Toxicology* **40**, 405–421.
34. **Efferth T *et al.*** (2003) Molecular modes of action of artesunate in tumor cell lines. *Molecular Pharmacology* **64**, 382–394.
35. **Ho WE *et al.*** (2014) Artemisinins: pharmacological actions beyond antimalarial. *Pharmacology & Therapeutics* **142**, 126–139.
36. **Krishna S *et al.*** (2015) A randomised, double blind, placebo-controlled pilot study of oral artesunate therapy for colorectal cancer. *EBioMedicine* **2**, 82–90.
37. **Efferth T** (2015) Artemisinin – second career as anticancer drug? *World Journal of Traditional Chinese Medicine* **1**, 2–25.
38. **Li J *et al.*** (2017) Artemisinins target GABAA receptor signaling and impair $\alpha$ cell identity. *Cell* **168**, 1–15.
39. **Posner GH and O'Neill PM** (2004) Knowledge of the proposed chemical mechanism of action and cytochrome p450 metabolism of antimalarial trioxanes like artemisinin allows rational design of new antimalarial peroxides. *Accounts of Chemical Research* **37**, 397–404.
40. **O'Neill PM *et al.*** (2010) The molecular mechanism of action of artemisinin – the debate continues. *Molecules* **15**, 1705–1721.
41. **Stocks PA *et al.*** (2007) Evidence for a common non-heme chelatable-iron-dependent activation mechanism for semisynthetic and synthetic endoperoxide antimalarial drugs. *Angewandte Chemie International Edition in English* **46**, 6278–6283.
42. **Wang J *et al.*** (2015) Haem-activated promiscuous targeting of artemisinin in *Plasmodium falciparum*. *Nature Communications* **6**, 10111.
43. **Zhou Y *et al.*** (2016) Profiling of multiple targets of artemisinin activated by hemin in cancer cell proteome. *ACS Chemical Biology* **11**, 882–888.
44. **Posner GH *et al.*** (1994) Mechanism-based design, synthesis, and in vitro antimalarial testing of new 4-methylated trioxanes structurally related to artemisinin: the importance of a carbon-centered radical for antimalarial activity. *Journal of Medicinal Chemistry* **37**, 1256–1258.
45. **Jefford CW *et al.*** (1995) The decomposition of cis-fused cyclopenteno-1,2,4-trioxanes induced by ferrous salts and some oxophilic reagents. *Helvetica Chimica Acta* **78**, 452–458.
46. **Wu W-M *et al.*** (1998) Unified mechanistic framework for the Fe (II)-induced cleavage of Qinghaosu and derivatives/analogues. The first spin-trapping evidence for the previously postulated secondary C-4 radical. *Journal of the American Chemical Society* **120**, 3316–3325.
47. **Haynes RK *et al.*** (2007) The $Fe^{2+}$-mediated decomposition, PfATP6 binding, and antimalarial activities of artemisone and other artemisinins: the unlikelihood of C-centered radicals as bioactive intermediates. *ChemMedChem* **2**, 1480–1497.
48. **Zhang S and Gerhard GS** (2008) Heme activates artemisinin more efficiently than hemin, inorganic iron, or hemoglobin. *Bioorganic & Medicinal Chemistry* **16**, 7853–7861.
49. **Meunier B and Robert A** (2010) Heme as trigger and target for trioxane-containing antimalarial drugs. *Accounts of Chemical Research* **43**, 1444–1451.
50. **Lew VL** (2003) Excess hemoglobin digestion and the osmotic stability of *Plasmodium falciparum*-infected red blood cells. *Blood* **101**, 4189–4194.
51. **Klonis N *et al.*** (2011) Artemisinin activity against plasmodium falciparum requires hemoglobin uptake and digestion. *Proceedings of the National Academy of Sciences of the United States of America* **108**, 11405–11410.
52. **Fitch CD *et al.*** (1983) Intracellular ferriprotoporphyrin IX is a lytic agent. *Blood* **62**, 1165–1168.
53. **Egan TJ** (2008) Recent advances in understanding the mechanism of hemozoin (malaria pigment) formation. *Journal of Inorganic Biochemistry* **102**, 1288–1299.
54. **Cazelles J *et al.*** (2001) Alkylation of heme by artemisinin, an antimalarial drug. *Comptes Rendus de l'Académie des Sciences - Series IIC – Chemistry* **4**, 85–89.
55. **Robert A *et al.*** (2005) The antimalarial drug artemisinin alkylates heme in infected mice. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 13676–13680.
56. **Loup C *et al.*** (2007) Trioxaquines and heme-artemisinin adducts inhibit the in vitro formation of hemozoin better than chloroquine. *Antimicrobial Agents and Chemotherapy* **51**, 3768–3770.
57. **Bousejra-El Garah F *et al.*** (2008) The antimalarial trioxaquine DU1301 alkylates heme in malaria-infected mice. *Antimicrobial Agents and Chemotherapy* **52**, 2966–2969.
58. **Yang YZ *et al.*** (1994) Alkylation of proteins by artemisinin. Effects of heme, pH, and drug structure. *Biochemical Pharmacology* **48**, 569–573.
59. **Meshnick SR** (2002) Artemisinin: mechanisms of action, resistance and toxicity. *International Journal for Parasitology* **32**, 1655–1660.
60. **Bhisutthibhan J *et al.*** (1998) The *Plasmodium falciparum* translationally controlled tumor protein homolog and its reaction with the antimalarial drug artemisinin. *Journal of Biological Chemistry* **273**, 16192–8.
61. **Eckstein-Ludwig U *et al.*** (2003) Artemisinins target the SERCA of *Plasmodium falciparum*. *Nature* **424**, 957–961.
62. **Arnou B *et al.*** (2011) The plasmodium falciparum $Ca^{(2+)}$-ATPase PfATP6: insensitive to artemisinin, but a potential drug target. *Biochemical Society Transactions* **39**, 823–831.
63. **Li W *et al.*** (2016) Characterization of the artemisinin binding site for translationally controlled tumor protein (TCTP) by Bioorthogonal Click Chemistry. *Bioconjugate Chemistry* **27**, 2828–2833.
64. **Kwong YL and Todd D** (1997) Delicious poison: arsenic trioxide for the treatment of leukemia. *Blood* **89**, 3487–3488.
65. **Jolliffe DM** (1993) A history of the use of arsenicals in man. *Journal of the Royal Society of Medicine* **86**, 287–289.
66. **Emadi A and Gore SD** (2010) Arsenic trioxide – an old drug rediscovered. *Blood Reviews* **24**, 191–199.
67. **Chen GQ *et al.*** (1996) In vitro studies on cellular and molecular mechanisms of arsenic trioxide ($As_2O_3$) in the treatment of acute promyelocytic leukemia: $As_2O_3$ induces $NB_4$ cell apoptosis with downregulation of Bcl-2 expression and modulation of PML-RAR alpha/PML proteins. *Blood* **88**, 1052–1061.
68. **Chen GQ *et al.*** (1997) Use of arsenic trioxide ($As_2O_3$) in the treatment of acute promyelocytic leukemia (APL). I. $As_2O_3$ exerts dose-dependent dual effects on APL cells. *Blood* **89**, 3345–3353.


https://doi.org/10.1017/erm.2018.3 Published online by Cambridge University Press

69. **Shen ZX *et al.*** (1997) Use of arsenic trioxide ($As_2O_3$) in the treatment of acute promyelocytic leukemia (APL). II. Clinical efficacy and pharmacokinetics in relapsed patients. *Blood* **89**, 3354–3360.
70. **Rao Y *et al.*** (2013) A drug from poison: how the therapeutic effect of arsenic trioxide on acute promyelocytic leukemia was discovered. *Science China Life Sciences* **56**, 495–502.
71. **Huang ME *et al.*** (1988) Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. *Blood* **72**, 567–572.
72. **Wang Z-Y and Chen Z** (2008) Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood* **111**, 2505–2515.
73. **Griffin JD** (2016) Bloods 70th anniversary: arsenic--from poison pill to magic bullet. *Blood* **127**, 1729–1730.
74. **Soignet SL *et al.*** (1998) Complete remission after treatment of acute promyelocytic leukemia with arsenic trioxide. *New England Journal of Medicine* **339**, 1341–1348.
75. **Niu C *et al.*** (1999) Studies on treatment of acute promyelocytic leukemia with arsenic trioxide: remission induction, follow-up, and molecular monitoring in 11 newly diagnosed and 47 relapsed acute promyelocytic leukemia patients. *Blood* **94**, 3315–3324.
76. **Shen Z-X *et al.*** (2004) All-trans retinoic acid/$As_2O_3$ combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 5328–5335.
77. **Estey E *et al.*** (2006) Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood* **107**, 3469–3473.
78. **Lo-Coco F *et al.*** (2013) Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *New England Journal of Medicine* **369**, 111–121.
79. **Efficace F *et al.*** (2014) Randomized phase III trial of retinoic acid and arsenic trioxide versus retinoic acid and chemotherapy in patients with acute promyelocytic leukemia: health-related quality-of-life outcomes. *Journal of Clinical Oncology* **32**, 3406–3412.
80. **Zhang T *et al.*** (2001) Arsenic trioxide, a therapeutic agent for APL. *Oncogene* **20**, 7146–7153.
81. **Breccia M and Lo-Coco F** (2012) Arsenic trioxide for management of acute promyelocytic leukemia: current evidence on its role in front-line therapy and recurrent disease. *Expert Opinion on Pharmacotherapy* **13**, 1031–1043.
82. **Jing Y *et al.*** (1999) Arsenic trioxide selectively induces acute promyelocytic leukemia cell apoptosis via a hydrogen peroxide-dependent pathway. *Blood* **94**, 2102–2111.
83. **Larochette N *et al.*** (1999) Arsenite induces apoptosis via a direct effect on the mitochondrial permeability transition pore. *Experimental Cell Research* **249**, 413–421.
84. **Kitamura K *et al.*** (2000) Involvement of CD95-independent caspase 8 activation in arsenic trioxide-induced apoptosis. *Leukemia* **14**, 1743–1750.
85. **Cai X *et al.*** (2000) Arsenic trioxide-induced apoptosis and differentiation are associated respectively with mitochondrial transmembrane potential collapse and retinoic acid signaling pathways in acute promyelocytic leukemia. *Leukemia* **14**, 262–270.
86. **Belzacq AS *et al.*** (2001) Adenine nucleotide translocator mediates the mitochondrial membrane permeabilization induced by lonidamine, arsenite and CD437. *Oncogene* **20**, 7579–7587.
87. **Miller WH *et al.*** (2002) Mechanisms of action of arsenic trioxide. *Cancer Research* **62**, 3893–3903.
88. **Dai J *et al.*** (1999) Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox system. *Blood* **93**, 268–277.
89. **Kapahi P *et al.*** (2000) Inhibition of NF-κB activation by arsenite through reaction with a critical cysteine in the activation loop of IκB kinase. *Journal of Biological Chemistry* **275**, 36062–36066.
90. **Davison K *et al.*** (2002) Arsenic trioxide: mechanisms of action. *Seminars in Hematology* **39**, 3–7.
91. **de Thé *et al.*** (1990) The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. *Nature* **347**, 558–561.
92. **Dyck JA *et al.*** (1994) A novel macromolecular structure is a target of the promyelocyte-retinoic acid receptor oncoprotein. *Cell* **76**, 333–343.
93. **Wang ZG *et al.*** (1998) PML is essential for multiple apoptotic pathways. *Nature Genetics* **20**, 266–272.
94. **Melnick A and Licht JD** (1999) Deconstructing a disease: RARalpha, its fusion partners, and their roles in the pathogenesis of acute promyelocytic leukemia. *Blood* **93**, 3167–3215.
95. **Zhu J *et al.*** (2001) Pathways of retinoic acid- or arsenic trioxide-induced PML/RARalpha catabolism, role of oncogene degradation in disease remission. *Oncogene* **20**, 7257–7265.
96. **Lallemand-Breitenbach V *et al.*** (2001) Role of promyelocytic leukemia (PML) sumolation in nuclear body formation, 11S proteasome recruitment, and $As_2O_3$-induced PML or PML/retinoic acid receptor alpha degradation. *Journal of Experimental Medicine* **193**, 1361–1371.
97. **Jeanne M *et al.*** (2010) PML/RARA oxidation and arsenic binding initiate the antileukemia response of $As_2O_3$. *Cancer Cell* **18**, 88–98.
98. **Zhang X-W *et al.*** (2010) Arsenic trioxide controls the fate of the PML-RAR alpha oncoprotein by directly binding PML. *Science* **328**, 240–243.
99. **Shao W *et al.*** (1998) Arsenic trioxide as an inducer of apoptosis and loss of PML/RAR alpha protein in acute promyelocytic leukemia cells. *Journal of the National Cancer Institute* **90**, 124–133.
100. **Ghaffari SH *et al.*** (2012) Alteration in miRNA gene expression pattern in acute promyelocytic leukemia cell induced by arsenic trioxide: a possible mechanism to explain arsenic multi-target action. *Tumour Biology* **33**, 157–172.
101. **de Thé H and Chen Z** (2010) Acute promyelocytic leukaemia: novel insights into the mechanisms of cure. *Nature Reviews Cancer* **10**, 775–783.
102. **Efferth T *et al.*** (2007) From traditional Chinese medicine to rational cancer therapy. *Trends in Molecular Medicine* **13**, 353–361.
103. **Youns M *et al.*** (2010) Traditional Chinese medicines (TCMs) for molecular targeted therapies of tumours. *Current Drug Discovery Technologies* **7**, 37–45.
104. **Li X *et al.*** (2007) Western-medicine-validated anti-tumor agents and traditional Chinese medicine. *Trends in Molecular Medicine* **14**(1), 1–2.
105. **Li SG *et al.*** (2013) The efficacy of Chinese herbal medicine as an adjunctive therapy for advanced non-small cell lung cancer: a systematic review and meta-analysis. *PLoS ONE* **8**, e57604.
106. **Chung VCH *et al.*** (2015) Effectiveness of Chinese herbal medicine for cancer palliative care: overview of systematic reviews with meta-analyses. *Scientific Reports* **5**, 18111.
107. **Chung VCH *et al.*** (2016) Chinese herbal medicine for symptom management in cancer palliative care: systematic review and meta-analysis. *Medicine* (*Baltimore*) **95**, e2793.
108. **Liu S and Cheng Y** (2012) Old formula, new Rx: the journey of PHY906 as cancer adjuvant therapy. *Journal of Ethnopharmacology* **140**, 614–623.
109. **Farrell MP and Kummar S** (2003) Phase I/IIA randomized study of PHY906, a novel herbal agent, as a modulator of chemotherapy in patients with advanced colorectal cancer. *Clinical Colorectal Cancer* **2**, 253–256.
110. **Saif MW *et al.*** (2014) First-in-human phase II trial of the botanical formulation PHY906 with capecitabine as second-line therapy in patients with advanced pancreatic cancer. *Cancer Chemotherapy and Pharmacology* **73**, 373–380.
111. **Tong X *et al.*** (2012) Treatment of diabetes using traditional Chinese medicine: past, present and future. *American Journal of Chinese Medicine* **40**, 877–886.
112. **Li WL *et al.*** (2004) Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. *Journal of Ethnopharmacology* **92**, 1–21.
113. **Yin J *et al.*** (2012) Effects and mechanisms of berberine in diabetes treatment. *Acta Pharmaceutica Sinica B* **2**, 327–334.
114. **Chen QM and Xie MZ** (1986) Studies on the hypoglycemic effect of *Coptis chinensis* and berberine. *Yao Xue Xue Bao* **21**, 401–406.
115. **Ni YX** (1988) Therapeutic effect of berberine on 60 patients with type II diabetes mellitus and experimental research. *Zhong Xi Yi Jie He Za Zhi* (*Chinese Journal of Modern Developments in Traditional Medicine*) **8**, 711–713.
116. **Yin J *et al.*** (2008) Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism* **57**, 712–717.
117. **Zhang Y *et al.*** (2008) Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. *Journal of Clinical Endocrinology and Metabolism* **93**, 2559–2565.


https://doi.org/10.1017/erm.2018.3 Published online by Cambridge University Press

118. **Dong H *et al.*** (2012) Berberine in the treatment of type 2 diabetes mellitus: a systemic review and meta-analysis. *Evidence-Based Complementary and Alternative Medicine* **2012**, 591654.
119. **Lan J *et al.*** (2015) Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. *Journal of Ethnopharmacology* **161**, 69–81.
120. **Pang B *et al.*** (2015) Application of berberine on treating type 2 diabetes mellitus. *International Journal of Endocrinology* **2015**, 905749.
121. **Yang J *et al.*** (2012) Berberine improves insulin sensitivity by inhibiting Fat store and adjusting adipokines profile in human preadipocytes and metabolic syndrome patients. *Journal of Evidence-Based Complementary & Alternative Medicine* **2012**, 1–9.
122. **Kong W-J *et al.*** (2009) Berberine reduces insulin resistance through protein kinase C-dependent up-regulation of insulin receptor expression. *Metabolism* **58**, 109–119.
123. **Lee YS *et al.*** (2006) Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. *Diabetes* **55**, 2256–2264.
124. **Yin J *et al.*** (2002) Effects of berberine on glucose metabolism in vitro. *Metabolism* **51**, 1439–1443.
125. **Pan G-Y *et al.*** (2003) The antihyperglycaemic activity of berberine arises from a decrease of glucose absorption. *Planta Medica* **69**, 632–636.
126. **Han J *et al.*** (2011) Modulating gut microbiota as an anti-diabetic mechanism of berberine. *Medical Science Monitor* **17**, RA164–167.
127. **Zhou J-Y and Zhou S-W** (2011) Protective effect of berberine on antioxidant enzymes and positive transcription elongation factor b expression in diabetic rat liver. *Fitoterapia* **82**, 184–189.
128. **Ni W-J *et al.*** (2015) Berberine as a promising anti-diabetic nephropathy drug: an analysis of its effects and mechanisms. *European Journal of Pharmacology* **760**, 103–112.
129. **Vuddanda PR *et al.*** (2010) Berberine: a potential phytochemical with multispectrum therapeutic activities. *Expert Opinion on Investigational Drugs* **19**, 1297–1307.
130. **Ji L *et al.*** (2013) Efficacy and safety of traditional Chinese medicine for diabetes: a double-blind, randomised, controlled trial. *PLoS ONE* **8**, e56703.
131. **Lin Y-J *et al.*** (2015) Chinese herbal medicine treatment improves the overall survival rate of individuals with hypertension among type 2 diabetes patients and modulates In vitro smooth muscle cell contractility. *PLoS ONE* **10**, e0145109.
132. **Liu Y *et al.*** (2012) Chinese herb and formulas for promoting blood circulation and removing blood stasis and antiplatelet therapies. *Evidence-Based Complementary and Alternative Medicine* **2012**, 184503.
133. **Ji XY *et al.*** (2000) *Salvia miltiorrhiza* and ischemic diseases. *Acta Pharmacologica Sinica* **21**, 1089–1094.
134. **Lei X *et al.*** (2014) Status and thoughts of Chinese patent medicines seeking approval in the US market. *Chinese Journal of Integrative Medicine* **20**, 403–408.
135. **Sun M *et al.*** (2009) Clinical observation of Danhong injection (herbal TCM product from radix *Salviae miltiorrhizae* and *Flos Carthami tinctorii*) in the treatment of traumatic intracranial hematoma. *Phytomedicine* **16**, 683–689.
136. **Liao P *et al.*** (2015) Danhong injection (a Traditional Chinese Patent Medicine) for acute myocardial infarction: a systematic review and meta-analysis. *Evidence-Based Complementary and Alternative Medicine* **2015**, 646530.
137. **Wang H *et al.*** (2016) An overview of systematic reviews of Danhong injection for ischemic stroke. *Evidence-Based Complementary and Alternative Medicine* **2016**, 8949835.
138. **Writing Group of Recommendations of Expert Panel from Chinese Geriatrics Society on the Clinical Use of Compound Danshen Dripping Pills** (2017) Recommendations on the clinical use of compound Danshen dripping pills. *Chinese Medical Journal (England)* **130**, 972–978.
139. **Wang XX *et al.*** (2007) New developments in the chemistry and biology of the bioactive constituents of Tanshen. *Medicinal Research Reviews* **27**, 133–148.
140. **Chan K *et al.*** (2004) Protective effects of Danshensu from the aqueous extract of *Salvia miltiorrhiza* (Danshen) against homocysteine-induced endothelial dysfunction. *Life Sciences* **75**, 3157–3171.
141. **Li P *et al.*** (2017) Toward a scientific understanding of the effectiveness, material basis and prescription compatibility of a Chinese herbal formula Dan-hong injection. *Scientific Reports* **7**, 46266.
142. **Zhou L *et al.*** (2005) Danshen: an overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. *Journal of Clinical Pharmacology* **45**, 1345–1359.
143. **Zhang N *et al.*** (2010) Biphasic effects of sodium danshensu on vessel function in isolated rat aorta. *Acta Pharmacologica Sinica* **31**, 421–428.
144. **Yu C *et al.*** (2014) Effects of Danshensu on platelet aggregation and thrombosis: in vivo arteriovenous shunt and venous thrombosis models in rats. *PLoS ONE* **9**, e110124.
145. **Ho J and Hong C-Y** (2011) Salvianolic acids: small compounds with multiple mechanisms for cardiovascular protection. *Journal of Biomedical Science* **18**, 30.
146. **Zhou X *et al.*** (2012) Danshensu is the major marker for the antioxidant and vasorelaxation effects of Danshen (*Salvia miltiorrhiza*) water-extracts produced by different heat water-extractions. *Phytomedicine* **19**, 1263–1269.
147. **Sun J *et al.*** (2005) Effects of purified herbal extract of *Salvia miltiorrhiza* on ischemic rat myocardium after acute myocardial infarction. *Life Sciences* **76**, 2849–2860.
148. **Lam FFY *et al.*** (2008) Dihydrotanshinone, a lipophilic component of *Salvia miltiorrhiza* (danshen), relaxes rat coronary artery by inhibition of calcium channels. *Journal of Ethnopharmacology* **119**, 318–321.
149. **Ren-an Q *et al.*** (2014) Study of the protective mechanisms of compound Danshen tablet (Fufang Danshen pian) against myocardial ischemia/reperfusion injury via the Akt-eNOS signaling pathway in rats. *Journal of Ethnopharmacology* **156**, 190–198.
150. **Cheng TO** (2007) Cardiovascular effects of Danshen. *International Journal of Cardiology* **121**, 9–22.
151 **Li X *et al.*** (2013) Traditional Chinese medicine in cancer care: a review of controlled clinical studies published in Chinese. *PLoS ONE* **8**, e60338.
152. **Ziegler S *et al.*** (2013) Target identification for small bioactive molecules: finding the needle in the haystack. *Angewandte Chemie International Edition* **52**, 2744–2792.
153. **Wang J *et al.*** (2016) Target identification of natural and traditional medicines with quantitative chemical proteomics approaches. *Pharmacology & Therapeutics* **162**, 10–22.


https://doi.org/10.1017/erm.2018.3 Published online by Cambridge University Press