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## Critical Review

## Natural Products & Complementary Medicines: Where are we up to?

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### ABSTRACT

The use of complementary and alternative medicine (CAM) has attracted much attention in recent years and has become a significant topic of debate within the healthcare sector. Many patients suffering from serious conditions such as cancer, Alzheimer's disease, diabetes and lower back pain seek alternative therapies including CAM biological products. Clinicians and healthcare practitioners need to be aware of the available clinical evidence relating to CAM-based therapies when advising patients and recommending options. This review presents the recent clinical data investigating the efficacy of CAM therapies for disease management among these groups of patients. A number of cancer drugs are listed which have been developed from natural sources and which have recently gained approval from the EMA and FDA based on clinical trials. Reasons for using CAM and the most frequently used CAM therapies are mentioned as well as the degree of improvement of quality of life based on patients' experiences.

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### INTRODUCTION

According to National Institutes of Health, complementary and alternative medicine (CAM) is defined as a group of heterogeneous group of medical and healthcare systems, substances, supplements and procedures that do not count to be a part of mainstream of conventional medicine (Baruah, Borua et al. 2016). These include medication-based therapies in which herbal or mineral products are used and non-medication practices such as acupuncture, aromatherapy, Ayurvedic medicine, massage, chiropractic and osteopathy (Hyodo, Amano et al. 2005).

According to the World Health Organisation (WHO), around 80% of the world's population depends on indigenous therapy that is closely correlated with CAM (Lim, Sadarangani et al. 2005). The use of CAM

is widespread in many countries, such as Australia and the UK. CAM has been used by almost 40% of adults in the US, 50% in Canada, and 75% in France (Bradshaw 2016; Jatau, Aung et al. 2016). In the UK, the prevalence rate of CAM use among the general population is about 46%, that is, where one or more CAM therapies are used during a lifetime (Bishop and Lewith 2010). The availability of CAM treatments via the National Health Service (NHS) provisions has increased significantly in the UK and the NHS currently provides funds for the following therapies: herbal medicine, acupuncture, homeopathy, osteopathy and chiropractic (Thomas and Coleman 2004). However, many other CAM-based therapies are offered outside NHS provision (Thomas, Coleman et al. 2001).

Why have CAM-based therapies increased in popularity among patients with serious diseases? There are several reasons for trying this kind of

medicine, including perceived effectiveness, accessibility, affordability, improvements in physical and emotional wellbeing, prevention of ill health, desperation or dissatisfaction with some aspects of conventional medicine such as the cost and the adverse effect, a positive inclination towards it as well as its relaxing effects (Ernst and White 2000; Molassiotis, Fernandez-Ortega et al. 2005). It has been estimated that 96% of doctors have not been given basic knowledge of CAM therapies (Frass, Strassl et al. 2012). This may have resulted in communication gaps between clinicians and patients about the potential usefulness of CAM, leading to ineffective disease management.

In this review we highlight the usage of CAM therapies in cancer, Alzheimer's, diabetes and low back pain patients. We report the most frequently used CAM modalities and evaluate how these can facilitate the management of these dangerous diseases. Evidence from recently published clinical studies is cited in evaluating the effectiveness of CAM therapies among these groups of patients.

### **CAM and Cancer**

Despite the advances made by conventional medicine for cancer treatment, interest in CAM continues to grow at an exponential rate and its popularity in cancer care has been well documented (Chatwin and Tovey 2004). A survey conducted by researchers revealed that cancer patients began using CAM alongside conventional treatment because the latter sometimes fails to cure the majority of common cancers (Scott, Kearney et al. 2005). Patients also found that the CAM-based treatments are accessible, affordable and relatively safe when compared to conventional medicine (Oh, Butow et al. 2010; Erku 2016)

Interestingly, despite the demographic origin of the cancer patients, studies reveal that CAM users are generally well educated, with an overall higher standard of education than non-CAM users (Scott, Kearney et al. 2005; Farooqui, Hassali et al. 2015; Sullivan, Gilbar et al. 2015). It may be that those with higher educational qualifications are more inclined to investigate the potential benefits of new or alternative therapies, especially for serious diseases such as cancer.

Considering the type of CAM used, cancer patients may use one or more CAM modality in the management of their disease and there is clear regional variability in the choice of CAM modalities. In the UK, relaxation and meditation techniques, spiritual or faith healing, reflexology, aromatherapy, and mineral and herbal products are the most common modalities used by cancer patients (Scott, Kearney et al. 2005). In Malaysia, Japan, Palestine and Australia, nutritional supplements, herbal products and multivitamins are the most common CAM therapies (Hyodo, Amano et al. 2005; Farooqui, Hassali et al. 2015; Sullivan, Gilbar et al. 2015; Ali-Shtayeh, Jamous et al. 2016). Multivitamins are also regularly used in the US, as well as chiropractic or osteopathic manipulation, movement therapies, special diets; such as organic vegetables and fruit, gluten free, casein free, no processed sugars or no salicylates; acupuncture, naturopathy, or different combinations of these therapies (Shih, Chiang et al. 2009; Perrin, Coury et al. 2012; Falci, Shi et al. 2016). It is clear that these regional variations in the CAM preferences of cancer patients may be attributable to differences in cultures and traditions in terms of practices and food, e.g. in Asia some of the consumed food is low in fat, high in fibers and full of fresh fruits and vegetables, thus the most commonly used CAM is associated with nutritional supplements and multivitamins. From the literature, breast, lung and colorectal cancers are the most frequent diagnoses among CAM users (Scott, Kearney et al. 2005). It has been highlighted by several studies that patients using CAM in combination with conventional medicine were those in the more advanced stages of cancer. This is an indication that patients in the later stages are keen to try all possible therapies offered by healthcare professionals as they are often desperate to survive and have been fighting their disease for a long period of time (Sullivan, Gilbar et al. 2015).

It is apparent, then, that CAM-based therapies can help to improve the quality of life of cancer patients, and recent years have also witnessed the discovery for new anti-cancer compounds from natural sources. Such new compounds show structural diversity with great biological functionality. Furthermore, this chemical variety plays an important role in shaping the pharmacological diversity of compounds and interacting with multiple targets as cancer is known as a complex disease. In addition, the continuing

discovery of natural lead is paving the way for medicinal chemists to synthesise modified substances with similar or even stronger effects (Cragg and Pezzuto 2016). Therefore, scientist focus on searching of new anti-tumour agents from natural sources as many plant and marine derived compounds are successfully used in the clinic for cancer therapy. Taxol, vinblastine and camptothecin, for example, are well known examples of approved and successful plant-based drugs for cancer patients. Other natural sources, such as marine organisms (e.g. ecteinascidin 743 and halichondrin B) and microbes (e.g. bleomycin and doxorubicin), have also provided anti-tumour lead compounds (Cragg and Pezzuto 2016).

To approve that natural products are a continuous source of biologically active compounds, several anti-cancer compounds have recently been approved by the European Medical Association (EMA) and the Food and Drug Administration (FDA) (Basmadjian, Zhao et al. 2014; Newman and Cragg 2016). The compounds listed below (Table. 1) have either been isolated directly from their natural origin, modified from natural pharmacophores or obtained from natural sources, such as biological macromolecules, peptides or proteins isolated from living organisms/cell line.

#### *Istodax®*

Istodax® is a novel natural compound that was approved by the FDA for the treatment of patients with cutaneous T-cell lymphoma in 2009. This unique compound, romidepsin, was isolated from the Gram-negative *Chromobacterium violaceum*, which was isolated from a Japanese soil sample (VanderMolen, McCulloch et al. 2011). High response rates have been observed in a Phase II study of both cutaneous and peripheral T-cell lymphoma and a Phase III study is still ongoing in combination with several anti-tumour agents (Bates, Eisch et al. 2015).

#### *Kadcyla®*

This lead is a combination of trastuzumab coupled to emtansine, the latter is a maytansine derivative being a biosynthetic product of the *Putterlickia* spp. root-associated endophytic bacterial community (LoRusso, Weiss et al. 2011; Kusari, Kusari et al. 2016). The FDA has approved this natural compound in 2013 for HER2-positive metastatic breast cancers based on a Phase III study (Peddi and Hurvitz 2014).

#### *Halaven®*

This is a synthetic derivative inspired by a natural marine product, halichondrin B, which has been recently approved by the FDA. It has been named eribulin mesylate and works as a non-taxane microtubule dynamics inhibitor (Yu, Zheng et al. 2013). This marine-derived compound can be used to treat metastatic breast cancer, as a Phase III study has shown an elevation in survival rates of the tested population (Cortes, O'Shaughnessy et al. 2011).

#### *Kyprolis®*

Epoxomicin, isolated from *Actinomyces*, has been modified to obtain a new anti-tumour lead named carfilzomib (Meng, Mohan et al. 1999). This new derivative has shown to yield effective results with manageable toxicity in multiple myeloma patients, leading to its approval by the FDA in 2012 (Muchtar, Gatt et al. 2016).

#### *PICN (Paclitaxel derivative)*

PICN® is a new formulation of paclitaxel which contains polymer and lipid mixtures; that has been approved by the FDA in 2012 (Newman and Cragg 2016). This novel formulation offers efficacy and potential safety in breast cancer patients, as evaluated in a Phase III trial (Jain, Gupte et al. 2016).

#### *Biological macromolecule*

Biological macromolecule refers to a large peptide that either isolated from an organism or developed by biotechnological means in a surrogate host (Newman and Cragg 2016). Blincyto® is a biological macromolecule working as an immunotherapeutic antibody called blinatumomab. Its approval in 2014 is based on clinical trials involving B-cell acute lymphoblastic leukemia patients (Sheridan 2015).

Nivolumab and pembrolizumab are human IgG4 programmed death 1 antibodies which have been approved by the FDA in 2015 (Shu and Rizvi 2016). Phase III studies of nivolumab involving patients who had metastatic melanoma without BRAF mutation demonstrated significant improvements in melanoma patients (Robert, Long et al. 2015). The safety and efficacy of pembrolizumab was also shown in a study of metastatic melanoma and non-small-cell lung patients (Garon, Rizvi et al. 2015; Raedler 2015a). Ramucirumab, in the form of an IgG1 monoclonal antibody VEGFR-2 antagonist called Cyramza®, is an angiogenesis inhibitor (Fuchs, Tomasek et al. 2013;

Wang, Wang et al. 2015). It has been approved recently for the treatment of patients with advanced gastric or gastroesophageal junction adenocarcinoma (Fuchs, Tomasek et al. 2013).

### CAM and Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder and a major cause of dementia in the elderly. It is characterised by many features such as the deterioration of structure and/or function of neurons associated with functional disorders of language, memory, cognition, emotion, character and behaviour (Ip, Tsim et al. 2014; Liu, Kong et al. 2014). It has been reported that traditional herbal medicine products are the most popular CAM modality for this condition in comparison to other CAM-based therapies (Posadzki, Ernst et al. 2012).

The pathogenesis of Alzheimer's disease reveals that oxidative stress, depletion or inadequate synthesis of neurotransmitters and the rapid degradation of neurotransmitters in the synaptic cleft due to rapid enzyme action results in changes in the biological mechanisms of neurons, leading to symptoms of the disease (Rasool, Malik et al. 2014). Therefore, agents with anti-oxidative, anticholinesterase and stimulating acetylcholine release properties are useful. Many traditionally used medicinal plants have demonstrated complementary cognitive benefits in the treatment of Alzheimer's disease. Moreover, there is strong clinical evidence to support the use of herbal medicine in both the treatment and prevention of Alzheimer's disease (Liu, Kong et al. 2014).

The efficacy of traditional herbal medicine has been confirmed by laboratory studies leading to the isolation of bioactive phytochemicals. For example, isolated anti-oxidative compounds such as piperine, from *Piper nigrum*, and sinapine, from *Brassica* species, have been shown to be effective agents in neurodegenerative disorders (Rasool, Malik et al. 2014). Neuroprotective agents such as ginkgetin, ginkgolides-A and B, from *Ginkgo biloba*, and anticholinesterase candidates like harmine (from *Peganum harmala*), galantamine (from *Galanthus* spp.) as well as vasicine and vasicol (from *Adhatoda vasica*) have also demonstrated therapeutic effects in the treatment of Alzheimer's (Heinrich and Lee Teoh 2004; Yoo and Park 2012; Ali, Hamed et al. 2013;

Rasool, Malik et al. 2014). Moreover, these findings are further supported by clinical studies conducted recently in which *G. biloba* shows potential benefit in patients with Alzheimer's disease, including the improvement of cognitive function and activities of daily living (Yang, Wang et al. 2016). Also, natural compounds antagonizing glutamate receptors are reported such as huperzine A, derived from *Huperzia serrata* (Qian and Ke 2014).

### CAM and diabetes

Diabetes mellitus is a metabolic syndrome and one of the pandemic diseases, with a prevalence of 400 million around the world (Yang, Chang et al. 2015). In diabetes management, studies reveal that acupuncture, massage, exercise, and herbal products can offer satisfaction to diabetic patients and have been shown to be effective alongside prescribed conventional medication. The adoption rate of CAM therapies by diabetic patients is high, since many of these modalities are low-cost, easily available in the community and meet lifestyle requirements (Pumthong, Nathason et al. 2015).

Interestingly, the uptake of CAM therapies depends on their popularity within a given population; for example, CAM is commonly used in countries where herbal medicine is common practice in primary health care such as Palestine and India (Ali-Shtayeh, Jamous et al. 2012; Baruah, Borua et al. 2016). Conversely, CAM-based therapies have been shown to be used less frequently by diabetic patients in Australia (Sibbritt, Davidson et al. 2015).

Natural digestive enzyme inhibitor from plants have been widely used for the treatment of Type-II diabetes and approved by FDA like acarbose, isolated from a number of species of *Actinomycetes* (Al Sibae and McGuire 2009; Bedekar, Shah et al. 2010). Furthermore, human clinical studies have demonstrated the effectiveness of anti-diabetic herbs such as *Bidens pilosa*. The hypoglycemic effects of this plant alone or in combination with conventional anti-diabetic drugs include reduction of fasting blood glucose and increase of fasting insulin levels. Importantly, as safety is a major issue with herbal products, the clinical data demonstrate clearly that *B. pilosa* formulation is safe in healthy subjects (Yang, Chang et al. 2015).

Table 1. List of anti-cancer compounds from natural sources which have been recently approved based on clinical trials.

Trade name	Generic name	Cancer type	Clinical studies	EMA/FDA approval
Istodax	Romidepsin	Cutaneous and peripheral T-cell lymphoma	I,II,III	Yes
Kadcyla	Trastuzumab emtansine	HER2-positive metastatic breast cancer	I,II,III	Yes
Halaven	Eribulin mesylate	Metastatic breast cancer	I,II,III	Yes
Kyprolis	Carfilzomib	Multiple myeloma	I,II,III	
PICN	Paclitaxel nanoparticle	Breast cancer	I,II,III	FDA
Blinicyto	Blinatumomab	B-cell acute lymphoblastic leukaemia	I,II,III	Yes
Optivo	Nivolumab	Metastatic melanoma without BRAF mutation	I,II,III	Yes
Keytruda	Pembrolizumab	Metastatic melanoma and non-small-cell lung cancer	I,II,III	Yes
Cyramza	Ramucirumab	Advanced gastric or gastroesophageal junction adenocarcinoma	I,II,III	Yes

### CAM and back pain

The problem of lower back pain is of great cost to health services as sufferers comprise the second largest group seeking primary care consultation in industrial countries (Quinn, Hughes et al. 2006). Osteopathy, chiropractic and massage are the most frequently accessed therapies for low back pain, and there is evidence to support their effectiveness (Murthy, Sibbritt et al. 2015). Acupuncture, herbal medicine, yoga and homeopathy are also reported to be popular CAM choices for this condition (Murthy, Adams et al. 2015).

Randomised controlled trials have been conducted on low back pain sufferers who were exposed to chiropractic manipulative therapy in conjunction with standard therapy, consisting of medication and general home care advice. Researchers concluded that the addition of chiropractic manipulation improved physical functioning in the tested population and demonstrated a significant advantage in the reduction of back pain compared to those receiving the standard therapy alone (Goertz, Long et al. 2013). The effect of yoga practice is also studied in low back pain patients and is found to offer good short-term effectiveness and moderate long-term effectiveness in controlled trials (Cramer, Lauche et al. 2013).

### CONCLUSIONS

The use of CAM is very well documented by a substantial proportion of patients suffering from serious diseases such as cancer, neurodegenerative disorders, diabetes and lower back pain. This review has provided valuable insights into the prevalence of CAM use, the most commonly used CAM modalities, and clinical studies approving its efficacy among these groups of patients. There is evidence that natural sources can provide novel and structurally diverse chemical compounds possessing anti-cancer properties and many have been approved recently by the EMA and FDA, for example, Kadcyla® and Istodax®. Although there is beneficial effects of using CAM as shown here based on clinical studies, there is lack of useful and effective communication between clinicians and patients about CAM therapies, since many CAM users engage in this kind of treatment without consulting their orthodox healthcare providers (Hyodo, Amano et al. 2005; Evans, Shaw et al. 2007). This is one of the factors which has led to the debate among healthcare practitioners about the place of CAM within the framework of mainstream medicine (Kissane, Bultz et al. 2011).

It is clear that patients with serious conditions as mentioned here have tried any of CAM modalities

based on personal preference but how can this CAM practice be engaged efficiently in the framework of health care and been prescribed by healthcare professionals. For this debate and to address this issue, a research strategy is needed to evaluate the efficacy of commonly used therapies, patient's attitudes regarding CAM, the effects of CAM outcomes and the safety of CAM. Also, this is required to identify the most relevant CAM therapies for specific clinical settings, to personalise this treatment and to understand user experiences (Fischer, Lewith et al. 2014). The outcome of this research will pave the way to make a stronger contribution to the need of patients and healthcare professionals enabling the engagement of CAM in healthcare framework.

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