

Complementary and Alternative Medicine (CAM) and the Public Health: an Innovative Healthcare Practice in Supporting and Sustaining Health and Well-Being

Andrew F Long*

*Professor, Health Systems Research, School of Healthcare, Rm 1.11 Baines Wing, University of Leeds, Leeds, UK

Abstract

Healthcare services across Europe face increasing pressure on service provision within a context of tight resource constraints, population ageing, an ever-increasing burden of chronic illness and multiple co-morbidities. However, a very low, average of 3% of resources is spent on prevention. With the publication of Health 2020, a resurgence of public health, with its focus on promoting and protecting the health of communities, becomes a real possibility. This paper explores the potential of Complementary and Alternative Medicine (CAM) as an innovative practice to enhance health and well-being, and thus public health. Beginning with an overview of CAM's core values and principles and evidence on its prevalence and user popularity, the paper focuses on the need to extend the notion of what counts as an outcome and the criticality of model validity in evaluating any CAM. Research evidence is presented on the potential value of CAM, with particular focus on findings from two case studies, one of traditional acupuncture, illustrating the importance of assessing outcome patterns, and the other of shiatsu illustrating the potential for enhancing critical health literacy. The set of emerging evidence points to CAM's potential to develop clients' critical health literacy, through enhancing awareness of the mind-body-lifestyle inter-connections and supporting enhanced control over their own lives. It argues that CAM has major potential to complement and add to individuals' healing practices with a view to its provision within integrative healthcare practice.

Keywords: CAM; Public health; Shiatsu; Acupuncture; Well-being; Critical health literacy

Introduction

Public health is commonly defined as 'the science and art of preventing disease, prolonging life and promoting health through the organised efforts of society' [1]. It centres on promoting and protecting the health of communities, individual citizens and the wider population. Epidemiology with its focus on exploring and identifying the determinants of ill-health and why and how some stay healthy [2], and by extension health inequalities [3] is a core contributory discipline generating evidence on influences, causes and potential ways to break the causal chain, thus enhancing health.

In a European context where a cross-country average of 3% is spent on prevention [4] one must question why a greater proportion of healthcare expenditure is not targeted and invested 'upstream' with a view to addressing the root socio-economic and cultural causes of ill-health and health inequalities, thus, intervening with whom or whatever is 'pushing them into the river'. The difficulty of such a funding and policy action is compounded by population ageing and increased survival, accompanied by an increasing burden of chronic illness and associated co-morbidity [4] all to be addressed within tight resource constraints. There remains the urgent imperative to treat and care for those 'downstream', 'pulling them out of the river'.

With the publication of Health 2020 [5] and its approval by the 53 countries within the European health region at a session of the WHO Regional Committee for Europe in September 2012, a higher priority for a shift in focus and resurgence of public health arises. This policy framework aims to 'significantly improve the health and well-being of populations, reduce health inequalities, strengthen public health and ensure people-centred health systems.' (ibid, p1). It identifies four priority areas for policy action, throughout emphasising 'developing assets and resilience within communities, empowerment and creating supportive environments.' (ibid, pvi). Public health is identified as the

third priority area, drawing attention to the importance of investing in health through the life-course, in order to empower and create resilience in supportive environments. As Dr Zsuzsanna Jakab, WHO Regional Director for Europe, argued at the fourth annual conference of the [6] European Public Health Alliance (2013), 'today's health emphasis is on non-communicable diseases and mental health problems. Also important is health-related behaviour, including tobacco and alcohol use, diet and physical activity: behaviour, which is itself socially determined and often reflects the stresses and disadvantages in people's lives.' The challenge of converting this political/policy level rhetoric into implementation and practical action remains to be realised.

Public health and Health 2020 (WHO 2013) draw explicit attention both to the social determinants of ill-health and the role of individuals and communities in enabling health. Associated notions include health promotion, empowerment and health literacy, all potentially aimed and taken forward at an individual and community level. Health promotion, through public health and/or individual action such as healthy eating, not smoking and taking exercise, centres on 'increasing people's control over their health and its determinants' [7]. Enhancing health literacy, defined for example as 'a range of skills and competencies that people develop over time to seek out, comprehend, evaluate and use health information ... to make informed choices' [8]

***Corresponding author:** Andrew F Long, Professor, Health Systems Research, School of Healthcare, Rm 1.11 Baines Wing, University of Leeds, Leeds, UK, Tel: +44 (0)113 343 6250; Fax: +44 (0)113 343 1378; E-mail: a.f.long@leeds.ac.uk

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becomes a key priority. Health literacy is a possible risk factor of ill-health, leading to attempts to mitigate low health literacy; but it is also an asset to be developed [9], aiming to enhance individuals' sense of control over their own health and their health decision-making. This suggests a need to adopt a 'whole-person' conception and model of (ill-) health and well-being, centred on enhancing people's awareness of their own body, life-style (including diet and exercise) and self-resiliency within the context of individuals' socio-economic-political and cultural life-worlds [10]. Health literacy interventions centre on individuals within their own life-worlds and will lead onto a wider impact on population health. The initiative of 'health-promoting schools' provides one apt example. As [11] Macnab outlines, a 'whole-school' approach is proposed with a view to provide school children with increased awareness and knowledge to help them improve their own health and well-being, encourage them to adopt a healthy lifestyle and carry this knowledge into their own lives and onto their parents and throughout their lives. As Freedman et al. [12] argue, creating a population 'that is public health literate' and developing individuals' critical health literacy [13] needs to be a major priority, and thus a major 'upstream-targeted' strategy.

Against this background, the discussion paper explores the potential of Complementary and Alternative Medicine (CAM) as an innovative practice to enhance health and well-being. It begins by providing an overview of CAM's core values and principles and evidence on its prevalence, and thus user popularity. Following elaboration of the importance of choice of outcome measures and model validity in evaluating any CAM modality, attention turns to present some research evidence on the potential value of CAM, with particular focus on findings from research studies used as case studies, one of traditional acupuncture and another of shiatsu. In so doing, the paper argues for the potential contribution that CAM modalities can play in promoting health and well-being and enhancing critical health literacy in integrative healthcare provision.

Materials and Methods

A number of different sources informed this paper. Firstly, it draws on the work of eminent scholars in the field of CAM to draw out insights into its definition and core values. Secondly, selective research studies of the prevalence of CAM are used, drawing in particular on the most recent systematic review [14]. The review was undertaken by members of the European research network for complementary and alternative medicine, CAM brella (<http://CAMbrella.eu>), established under the European Union's Seventh Framework Programme. The group comprised 16 partner institutions from 12 European countries and focused on academic research into, but not the advocacy for, any CAM treatment. The third source uses two research studies which the author either led or was a co-investigator; these are used as case studies to demonstrate the innovative potential of CAM.

The first case study, undertaken in the modality of Traditional Chinese Medicine (TCM) acupuncture, provides insight into the issue of whole person and whole therapy effects [15,16] and the question of what might be appropriate outcomes in evaluating a CAM modality, giving primacy to the user/patient's perspective [17]. The case study explores experiences and perceived benefits to women with Early Breast Cancer (EBC) of a course of TCM (Traditional) Acupuncture (TA) treatment received alongside receipt of chemotherapy [18] an important sub-question was: what are the perceived outcomes the TA practitioners aim to achieve and what outcomes do women value from their treatment? The study involved a small-scale, longitudinal

qualitative study of 14 women with EBC who received up to ten TA sessions from one of two experienced TA practitioners. The women were recruited via their oncologist from two NHS hospital trusts in the North of England and practitioners provided treatment in one of four centres, including private practice. The practitioners were asked to approach treatment as they normally would, thus replicating real world practice (individualised diagnosis and treatment at each treatment). In-depth, intensive interviews were undertaken with the women before, during and post-therapy and with the practitioners before the initial and after the final treatment; the practitioners also kept treatment logs. A grounded theory approach to data analysis was used, with emphasis lying on uncovering meaning and exploring process and change over time. Full detail of the study methods can be found in Price [18,19].

The second case study, undertaken in the modality of shiatsu, a body-based life-energy therapy developed in Japan and influenced by Western knowledge, casts light on the potential of a CAM to enhance critical health literacy. The case study is situated within a wider research study which aimed to provide cross-European insight into patient-perceived experiences and effects of shiatsu [20]. The wider study used a longitudinal, observational study design. It was undertaken in three European countries (Austria, Spain and the UK), with accredited and experienced (≥ 2 years in practice) practitioners selected from their national Shiatsu Society, each of which was a member of the European Shiatsu Federation. The clients, all to be 18 years or over and receiving shiatsu for any reason were recruited by the practitioners. Following a pre-defined protocol, treatment was to be provided as in normal practice (individualised and reviewed at each treatment session). Treatment included direct energy-based bodywork and, as appropriate, advice-giving on lifestyle and other factors.

Data were collected by self-administered postal-questionnaires (professionally translated into the relevant language) at four points in time: initial ('baseline') recruitment, subsequent to the shiatsu session; four to six days after the initial shiatsu session; and 3 and 6 months later. The content of the questionnaires was grounded in an earlier two-country (Germany and the UK) interview-based study [21]. The questionnaires covered a range of shiatsu-specific and more general areas, such as advice received, changes made (at 3 and 6 months), client 'hopes' from having shiatsu and features of the client-practitioner relationship, and included space for verbatim comments. Data analysis was restricted to those clients who completed all four questionnaires. Over an eleven month period, 948 clients were recruited by 85 practitioners, and 633 clients completed all four questionnaires, a response rate of 67%. Full detail of the study methods can be found in [20] Long.

The case study [22] focuses on a sub-question which arose from a post-hoc investigation of the findings from the lens of critical health literacy. It examines the role of advice-giving and advice-taking over time, with the aim of generating a tentative explanatory framework for the way a CAM modality could enhance individuals' critical health literacy and thus enable and support wider population health benefit. The case study drew on data on factors associated with advice-giving, for example: what clients 'hoped to get from having shiatsu' (at baseline); features of the client-practitioner relationship and advice-giving 'in the (baseline) session'; changes made 'in their life as a result of having these shiatsu treatments' (at 3 and 6 months); and, if they had made any changes, in what area(s), chosen from a list of possibilities (for example, diet, exercise, rest and relaxation) and described 'any other changes' in the space provided.

Findings and Discussion

What is CAM?

CAM comprises a diverse set of modalities and multiple healing systems. It includes alternative systems of health and healing, involving alternative diagnostic approaches to conventional bio-medicine (for example, Traditional Chinese Medicine (TCM), TCM acupuncture, ayurvedic medicine, homoeopathy) and/or disciplines/modalities (for example, herbal medicine, massage, reflexology, Reiki, shiatsu). One commonly cited definition depicts CAM as 'a group of diverse medical and healthcare systems, practices and products that are not presently considered to be part of conventional (bio-) medicine' [23]. Another definition within the Cochrane Collaboration points to complementary medicine as 'include (ing) all such practices and ideas which are outside the domain of conventional medicine in several countries and defined by its users as preventing or treating illness, or promoting health and well-being. These practices complement mainstream medicine...' Yet others talk of mind-body interventions (yoga, Reiki, meditation), energy-related modalities (acupuncture, reflexology, shiatsu), body alignment (osteopathy, chiropractic), herbal medicine and nutrition, including dietary supplements available 'over the counter'.

CAM is thus an umbrella terms and multiple definitions are in use both in policy and practice discussions and in the published literature. Most importantly there is a perspective of its being complementary, and not necessarily alternative, to conventional medicine. It thus widens the possible options for individuals in resolving symptoms, coping with ill-health and promoting health and well-being. There is also a highly varied legal context for CAM across countries and diversity in the regulation of CAM practice [24,25]. In the UK, a 'right to practice' is enshrined in English common law and some CAM modalities are taking part in voluntary regulation with the Complementary and Natural Healthcare Council (<http://www.cnhc.org.uk/>). Commonly in Europe, the USA, Canada and Australia, CAM use is paid for by users, who choose to access particular CAM modalities for a range of reasons [26,27]. Some are pulled into CAM (attracted to its mode of practice, underlying whole treatment approach), others pushed (experiencing bad side effects from conventional treatments or these not working for them as well as they might), with some being 'last resort' users (tried everything else), others more 'pragmatic' (shopping around to use whatever will help) and yet others being 'committed' users with CAM as a preferred treatment option, though not necessarily only using CAM [28]. Finally, individual users may approach the CAM treatments expecting to be 'done to' or fixed (that is, an individual as a relatively passive recipient); yet others are pro-actively seeking to use it as a form and part of their own self-care (thus, taking an active role), and by implication be more 'open' or 'ready to change' [29,30], including to respond to initiatives to develop their health literacy.

CAM's core principles and values

Some common principles are evident within the different CAM modalities, all of which are highly apposite for the promotion of individual and community health and well-being: an emphasis on self-healing, holism (a 'whole health' systems approach to health), individualised diagnosis and treatment, treatment centred on the whole person (body, mind and spirit) in their own life context/socio-economic and politico-environment [31]. For many, a key focus lies on enhancing self-awareness. The core goal involves assisting individuals in uncovering their own healing potential and in opening them up to the possibility of change. Focus lies initially on treating the presenting reasons for seeking treatment (symptoms), then moving

onto uncovering the underlying problem (a root and branch approach) and assisting the individual to become more aware of their own health and ways to sustain health and well-being. Desired outcomes include: resolving initial symptoms; raising individuals' awareness and understanding of their own body and factors affecting this, in the context of their own life situation; maintaining good health; and, supporting good health practices.

CAM prevalence

There is good evidence of high citizen popularity and use of CAM. For example, a US study reported 65 visits monthly per 1000 population to a CAM practitioner, compared with 113 visits per 1000 to see a primary care physician [32]. Looking Europe-wide, the European Information Centre for CAM (undated) estimates that more than 100 million EU citizens are 'regular' users of CAM, used predominantly for the treatment of chronic conditions. There is however no definitive or accepted estimate of the prevalence of CAM across the European Union. Study reports are compounded by measurement differences; some report use 'over the last 24 hours', others 'during the last year' or 'ever use'. In addition, what is defined or measured as 'CAM use' varies (for example, whether 'prayer' is included or different forms of manual manipulation are differentiated), and whether or not the 'CAM' is provided by a practitioner who has undergone an extensive period of recognised and accredited education and training in the modality or a short course on the CAM technique (for example, needling).

Notwithstanding these difficulties, there are a number of valid and replicable national surveys of CAM prevalence. Thomas and Coleman [33] drawing on a national Omnibus survey covering England, Wales and Scotland, estimated that 10% of the general population had 'received any CAM in the last year' and 6.5% had used one of five main therapies: acupuncture, homoeopathy, chiropractic, osteopathy or herbal medicine. Other evidence can be found in systematic reviews. Frass et al. [34] reported that prevalence rates in each of the 16 included studies (including ones from the USA and Canada) ranged from 5-75%. The most commonly used therapies were chiropractic manipulation, herbal medicine, massage and homoeopathy.

To gain a better understanding of the prevalence of CAM in the EU, the CAM brella research network undertook a systematic review of 87 published studies on the prevalence of CAM within and across EU member states. Eardley et al. [14] concluded that 'CAM prevalence across the EU is problematic to estimate because studies are generally poor and heterogeneous. A consistent definition of CAM, a core set of CAMs with country specific variations and a standardised reporting strategy to enhance the accuracy of data pooling would improve reporting quality.' They inferred that across EU member countries the overall reported prevalence rate of 'any type of CAM at any time' ranged from 0.3% to 86%, with wide variation in prevalence rates in specific countries and for reported therapies. The top five most commonly reported therapies were: herbal medicine, homoeopathy, chiropractic, acupuncture and reflexology. Dietary supplements were also commonly used, though it was not evident if these were bought over the counter or prescribed within a CAM consultation.

It is important to reflect that this widespread usage and popularity of CAM is situated within a context of a slowly emerging evidence base of the benefits of particular CAM modalities, their safety, effectiveness and cost-effectiveness [35,36]. Moreover, individuals may be using CAM alongside conventional treatments and paying for their treatment. At the same time, there is a varying picture of the recognition of CAM and its benefits by medical practitioners, along with a reluctance to

mention or suggest exploring other treatment options such as CAM to their patients [37]. This co-exists with a hesitancy or avoidance by their patients to tell the medical practitioner either about their use of CAM or to ask about its possible benefits in treating the illness.

CAM as innovative healthcare practice

What then is the potential for complementary and/or alternative ways to treat and address ill-health and support and sustain health and healing? CAM practitioners are quite explicit about the potential that they see, as is evident from ways that they promote their particular modality and associated treatments. These talk in terms of their treatment: seeing the individual as a whole person in her/his life-world; addressing and helping with symptoms of particular conditions; getting to the root of the problem; maintaining and promoting a good sense of health and well-being; and supporting individuals to (re-) gain greater control over their health and finding ways to cope that work for them.

There is a strong body of emerging evidence to support these perceptions. To try to offset increasing poly-pharmacy (persons using five or more drugs at one time) increasingly evident in the context of older persons with multiple co-morbidities, estimated at 40% of US seniors, [38] Jacobs and Fisher point to evidence, for example, on the potential of mind-body interventions, to assist in stress reduction with consequent beneficial effects on blood pressure levels and risk of heart attacks. There is also good evidence of the effectiveness of acupuncture to treat chronic knee, low back and neck pain, and a potential role in treating gastro-oesophageal reflux disease. Alongside this explicit use of CAM modalities, the potential to reduce or avoid statin use is evident through sound and comprehensive self-care information. As they argue, this range of examples suggest the importance and need (and potential cost savings) of giving more attention to non-drug alternatives to address the challenges of multi-morbidity.

Evaluations of the effectiveness of CAM must however be cognisant of and address two major issues: outcome measures used in the evaluation study and model validity. Each is illustrated in the following two case studies. The first issue centres on 'what counts' as an effect/outcome. Long [17] argued that at least three broad types of effects need to be measured: those arising from (i) the philosophy of health and healing and mode of practice; (ii) the client-practitioner relationship; and (iii) the specific techniques used by the modality to enhance the healing process (for example, bodywork, needling). To these one must add effects arising from the wider treatment environment as a health environment [39]. Allied to this is the importance of exploring what patient's value, and thus recognising the credibility and validity of 'self-reported perceptions'. Moreover, in order to appropriately measure the effects of a particular CAM, modified or new (outcome) measurement tools may be a need to be developed [16,40] and potentially modality-specific tools.

The second issue, of model validity, is closely linked. As Verhoef et al. [16] powerfully argue in the context of the relevance of randomised controlled trials to CAM, CAM modalities tend to comprise whole systems of health and healing, including inter alia approaches to provide individualised diagnosis and treatment. This points to the criticality of evaluating the whole CAM modality system, as practised (for example, TA not sham acupuncture or point acupuncture [41,42], ensuring good model validity between the evaluation design and modality's theory and practice. Taking these two issues together suggests the importance for CAM evaluation research to assess the 'whole system' effects, not just the 'specific' effects, such as symptom resolution but on to effects that embrace the whole system and whole experience of treatment.

Case study one: Broadening outcomes perspective

In her wider research, [19] Price illustrated evidence from biomedical research in breast cancer on the high incidence of a wide range of symptom and treatment side-effects. In EBC, examples include nausea, insomnia and emotional upset, with Cancer-Related Fatigue (CRF) being most reported. However, rather than occurring singly and in isolation, women diagnosed with breast cancer tend to experience these symptoms in clusters (CRF and nausea and pain), at the same time as facing existential issues arising from their life-threatening diagnosis. Moreover, during chemotherapy these symptom clusters fluctuate unpredictably. However, much biomedical research measures the incidence or change in these symptoms/side-effects singly, one symptom at a time, not as a symptom cluster, and tends to measure them at one point in time. It would thus seem highly appropriate to explore the effect of a CAM modality (here, TA) with its whole-person orientation in helping to mollify these effects, alongside inducing other patient benefits and through a prospective study design.

In the small-scale longitudinal study [18], women reported both general ('feeling better generally') and specific benefits ('it helped with lots of different things', for example, bloating, sleep patterns, achy joints). They also talked about broader benefits (such as 'being more relaxed', 'more balanced', 'calmer', 'having more energy') and the anticipatory effect of receiving an intervention that they thought might be beneficial. A highly valued outcome was enabling coping through the alleviation of symptoms and increased well-being.

Through their model of practice, practitioners attempted to deal with the presented symptom clusters the women described, most commonly fatigue and emotional upset along with disturbed sleep. While addressing these multiple problems, the practitioners also sought to achieve broad, whole-person effects, in particular, drawing attention to 'enable coping'. Their focus lay on 'resolving outcome patterns' in response to the woman's reported symptom clusters. Such wider effects were strongly valued by the women, along with 'being able to have space and time' during the therapeutic encounter to develop resources to 'carry on as normal'.

This research provides a vivid demonstration of how the way the CAM whole-system effects are experienced and realised within a practice context. The findings demonstrated TA practitioners treating patient concerns, leading onto the achievement of broader, non-symptom specific outcomes. The women valued the whole experience of TA and reported receiving considerable benefit from it, providing further evidence of TA as a supportive treatment provided in an integrative manner for women during chemotherapy. Moreover, the research gives strong support to the argument for the need to look beyond single symptom resolution to outcome patterns and broader whole-person effects.

Case study two: Developing critical health literacy

Long's [20] longitudinal study provided cross-European evidence on client-reported effects, both positive and negative, of shiatsu over time, as delivered and received within routine practice for clients coming to shiatsu for whatever reason. The results demonstrated a set of interconnected and consistent evidence of client-perceived, beneficial effects in the short and longer term, as measured by changes in symptom severity, shiatsu-specific measures, the uptake of advice, primary care use, meeting expectations and satisfaction levels.

One key finding, raising the question of why and a need for further exploration, related to advice-giving and advice-taking. At baseline,

three-quarters of the 633 clients reported that they received advice from the shiatsu practitioner, on exercise, diet, posture, points to work on at home or other ways of self-care. At six months follow-up, around four-fifths reported making changes to their lifestyle 'as a result of having shiatsu treatment', including taking more rest and relaxation or exercise, changing their diet, reducing time at work and other changes such as increased body/mind awareness and levels of confidence and resolve.

To explore this question further, a sub-set of the data was reanalysed through the lens of health literacy and the key features of shiatsu's philosophy and mode of practice [22]. The study results point to clients' developing awareness and knowledge of the way they lived their lives (what they ate, exercise taken, self-care) and body awareness occurring through practitioners' giving tailored individualised advice in relation to the client's presenting reasons for treatment. Such advice-giving also occurred in a treatment context that clients described in highly positive terms, involving 'listening' and 'accepting' and treatment as being provided by a skilful, warm and trusted practitioner. Client reports of making substantial changes to their lifestyle 'as a result of having shiatsu' are indicative of acting on their knowledge onto emerging critical health literacy, leading to thoughtful health-related decision-making. For example, clients expressed enhanced self-confidence and 'being more able to help myself,' along with increased understanding and awareness of their body.

Building on the findings, [22] Long drew up an explanatory model of possible ways that a CAM therapy could contribute to health promotion with a view to guide future research. Key contextual (and enabling) factors suggested included 'openness' and 'readiness to change' previously experienced treatment benefits and a supportive treatment environment. Possible mechanisms or ways through which the experienced changes and benefits might be realised was argued to comprise: the nature and style of the treatment sessions; relationship-building; the practitioner and client working together; and experience of accumulated benefits from the treatments. Through working together, an enhanced sense of control was brought about, itself enabling critical health literacy.

Engagement with the practitioner and the CAM modality was thus critical, through being open to change and taking greater responsibility for their own health. The study thus points to the importance of features of the CAM modality (philosophy, model and mode of practice) together with the way it is delivered (treatment environment, features of the practitioner-client encounter) and characteristics of the client (seeking help, openness and Rollni to change) interacting to facilitating advice-taking and critical health literacy.

In conclusion, this paper aimed to provide insight into CAM, its core values, principles and key issues to address when evaluating any CAM modalities and presented emerging evidence on CAM's effectiveness and innovative potential in enabling, supporting and enhancing people's health and well-being and thus the public health. Emerging evidence demonstrates the CAM's potential to enhance healthcare systems, not just to resolve symptoms (in the short and longer term) but also to enable and promote personal and community health and well-being. Its mode of practice and engagement with the client (individualistic diagnosis and treatment, listening, hearing and sharing) and holistic orientation (seeking to address the underlying root of the presented symptoms) leads onto increasing self-awareness and understanding about the mind-body connection within the context of individuals' own life-worlds. In this manner CAM modalities are

enabling individuals to (re-)gain greater control and make active choices to support their own health and well-being.

This emerging evidence base raises the wider issue of increasing access to CAM through a closer relationship with the dominant, bio-medical healthcare system and for CAM to be accessed and used in conjunction with or alongside conventional care, in an integrative care model [43] for a person with an acute or chronic condition. But as Lovell [44] argues, healthcare providers (including funders) may need to learn more about CAM. Alongside, it is useful to note the findings from Willis and Rayner [45] who report that integrative medical practitioners are tending to adopt a public health stance in their work, re-orienting their focus from cure to prevention, with an increased focus on lifestyle and other advice within the context of the individual's life-world. Finally, one can only speculate on what the potential benefits might be for patients, enhanced critical health literacy and the public's health, if CAM modalities were routinely available within health systems, in a context of integrative, collaborative care, rather than as an add-on pursued by individuals seeking an alternative approach or trying to cope with side-effects of treatments [46,47].

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