



## Opinion paper

# Health services research as a framework for expanding a whole systems research agenda in complementary and integrative medicine: The example of intestinal permeability

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## ABSTRACT

**Introduction:** Two of the three pillars of evidence-based practice emphasise the importance of using the best available academic research and experience from clinical practice to inform patient care. This paper aims to outline the potential value of exploring and describing insights from clinical practice through health services research to inform whole system research.

**Methods:** Concepts and ideas were developed from non-systematic review of published literature and extensive academic and clinical experience within the disciplines of health services research and clinical trials.

**Results:** Through deductive reasoning, complementary and integrative medicine (CIM) practitioners may have identified new understanding of the management of disease not yet seen in published literature. The area where investigating CIM practitioners in clinical practice may advance the clinical understanding of particular conditions is extensive. For instance, increased intestinal permeability (IP) is speculated to be involved in diseases frequently seen within clinical practice. IP is considered multifactorial with involvement from genetic and environmental factors.

**Conclusions:** CIM practitioners report clinical experience in the management of digestive disorders; their practice wisdom may add new knowledge to the significance of IP within clinical practice and outline testing parameters. Furthermore, the whole system treatment approach used by CIM practitioners may provide insight into new options for the management of IP not known or shared in published literature. Investigating the approaches CIM practitioners use within clinical practice may provide advancements in the clinical understanding of IP and other conditions. Exploring clinical practice may identify new knowledge that may translate to improvement in patient care.

## 1. Introduction

Two of the three pillars of evidence-based practice emphasise the importance of using the best available academic research and experience from clinical practice to inform patient care. While these pillars can be viewed as independent of each other, drawing on insights from clinical practice, or practice wisdom, to inform clinical research may offer an opportunity for research advancements and the production of new knowledge [1,2]. Health services research (HSR) is a multi-disciplinary field of scientific investigation that studies the effects of various components of healthcare and their outcomes [3]. Although HSR has been mainly focused on conventional healthcare,

complementary and integrative medicine (CIM) research utilising a HSR model is growing [4]. An area where HSR can be utilised in CIM research includes observing CIM practitioners in clinical practice, describing trends and patterns surrounding healthcare and observing patients and their characteristics.

CIM practitioners utilise a whole system healthcare approach that involves the use of complex interventions for a variety of conditions and complements the HSR model of enquiry [5,6]. Like HSR, whole system research (WSR) is a research model that attempts to capture the complexity of interventions implemented within clinical practice and the nature of daily routine care [3]. In addition, WSR is patient-centred rather than disease-centred and may provide a framework to examine

**Abbreviations:** CIM, complementary and integrative medicine; HSR, health services research; IP, increased intestinal permeability; MLCK, myosin light chain kinase; TJ, tight junctions; TNF, tumor necrosis factor; WSH, whole system research

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the practice of CIM more accurately than traditional randomised control trials [7]. For these reasons, HSR has been presented as a research framework that offers unique opportunities to researchers interested in exploring CIM from the perspective of a whole systems approach [7]. However, HSR is relatively undervalued despite the potential merit in informing clinical trial design [8]. HSR does not dismiss the necessity for clinical trials but rather lays the foundations for clinical trials that are informed by the realities of daily routine care in the community [9]. The focus and framework of HSR varies between developing and developed countries, therefore the concepts discussed here are most relevant to developed countries [10].

It has been estimated that between 38 and 68% of individuals use some form of CIM [11,12] with 16–55% of CIM users visiting a CIM practitioner within a 12-month period [12]. In light of these figures, it is important for clinical research to consider the whole system healthcare approach underpinning CIM practice [13]. Experiences and practices of CIM clinicians may provide valuable foundations to inform the direction of future clinical research [14]. Unfortunately, within CIM only a limited number of conditions have been investigated using a WSR approach. These include multiple sclerosis [15], detoxification [16], anxiety [17], type 2 diabetes [13], and breast cancer [18]. Furthermore, limited research has been implemented applying a HSR framework which captures the clinical experience of CIM practitioners for these and other health conditions [19]. By addressing this gap and employing HSR to explore and describe the experience and approaches of CIM practitioners to managing complex health conditions, the research community may gain insights which can be used to inform clinical research and improve patient centred care [20–22].

We propose that investigating CIM practitioners in clinical practice may provide insights, which can further expand clinical research and advance disease management both within CIM and across conventional healthcare more generally. Therefore the purpose of this paper is to outline a basis through which HSR can be used to identify clinical practice insights that may then inform clinical research. Increased intestinal permeability (IP), an emerging health issue [23], is a relatively new concept to conventional medicine and will be used as an example. CIM practitioners see a variety of health conditions and diseases in clinical practice, with a particular interest in digestive disorders [24]. There is a long empirical history of CIM practitioners such as naturopaths treating the gut as a major principle of disease management [20,21]. This interest and experience in the clinical management of digestive disorders may result in CIM practitioners acquiring practice wisdom not yet presented in published literature but worthy of closer examination.

## 2. IP as an emerging health issue

The barrier within the small intestine is formed from a monolayer of epithelium cells along with the mucus and microbiome to form a physical and biochemical barrier, separating the internal and external environment [25]. Between the epithelium cells is the paracellular pathway, where tight junctions (TJ) [26], adherens junctions and desmosomes are formed by an array of highly regulated proteins. Within the paracellular pathway, TJ selectively allows the permeability of small molecules such as water, ions and solutes to pass while restricting absorption of larger molecules [25]. However, dysregulation of TJ permits larger molecules such as bacteria and dietary antigens to permeate the mucosa and is collectively referred as IP [23]. There is growing evidence that IP plays an important role in some areas of health and disease [23].

The clinical consequence and understanding of IP remain poorly understood. Researchers have devoted attention to IP over the last 30 years, however, there are still gaps in the understanding of this condition [27,28]. The pathogenesis of IP is considered to be multifactorial with involvement from genetics [29] and environmental factors, such as dietary intake [30], exercise habits [31], chemicals

exposure [32] and nutrient deficiencies [33]. Emerging evidence suggests larazotide acetate, a pharmaceutical agent that regulates TJ [26], temporarily reduces IP and is now in phase III clinical trials [34]. While this drug is undoubtedly a pharmaceutical advancement to assist with IP it only provides short-term assistance and current evidence does not suggest it resolves the pathological processes [34]. Whereas, clinical CIM texts point to treatment approaches that may be employed successfully in the management of IP but have not amassed a body of clinical evidence similar to their pharmacological counterpart [20,21]. Investigating IP through a HSR framework may provide further understanding to the components CIM practitioners associate with the pathogenesis of IP and thereby may lead to in vitro mechanistic research.

## 3. HSR may form the basis to understand the complex management of disease

There is a theoretical two-way relationship between IP and disease: where the disease itself may cause IP or IP may cause the disease or condition [35,36]. Whether IP is an epiphenomenon, precedes disease manifestation or is involved in the pathogenesis of disease remains unknown. The consequence of IP being associated with specific diseases is of particular interest to clinical practice. There is clinical evidence suggesting that reducing IP translates to improvement in disease severity and clinical symptoms [34]. In susceptible individuals, the major factors that have been found to coincide with IP are intestinal dysbiosis and inflammation [37]. These factors may also exacerbate the degree of IP in particular diseases such as liver disease [38]. The interrelationship between dysbiosis and inflammation to IP is an important aspect to consider when conducting clinical research and insights into the clinical manifestation of this relationship may be captured through HSR methodology.

The microbiome forms part of the biological barrier that maintains the intestinal integrity and contributes to intestinal homeostasis [25]. A disruption to this balance can lead to dysbiosis – the imbalance of microorganisms within the gastrointestinal system. Dysbiosis has been associated as a causative factor in IP and may also trigger inflammation [37,38]. Consequently, tumor necrosis factor (TNF), an inflammatory cytokine, can bind with the TNF-receptor activating myosin light chain kinase (MLCK) within the intestinal epithelial cells [39]. This chain of reactions then causes the TJ to rearrange which can lead to IP [39]. The intestinal inflammation along with systemic inflammatory cytokines, namely interleukin-6 and interleukin-8, may disrupt the microbiome by impairing both the commensal and pathogenic bacteria, resulting in dysbiosis [40–42]. During IP, inflammatory cytokines may be produced in response to the host's exposure to endotoxins [43,44]. As a consequence of IP and inflammation, the equilibrium of the microbiome is negatively affected and leads to dysbiosis [40–42]. Ultimately, IP is affected by a complex array of factors; thereby, the management of such a condition may require multiple treatment approaches concurrently. WSR provides an appropriate research method to explore such a hypothesis however; initially investigating the management of IP through HSR, may provide preliminary insights to inform more robust methodological design of WSR.

## 4. HSR insights from CIM clinical practice to advance clinical understanding

There are a number of areas where applying HSR approaches to the examination of CIM clinical practice may advance the clinical understanding of IP. This is not a definitive list but rather an exploration of the breadth and depth of insights which CIM practitioners' knowledge, experience and practice wisdom may advance future research directed towards the clinical understanding of disease management in general, and IP in particular.

#### 4.1. The clinical significance of diseases and disease processes

CIM practitioners employ a holistic understanding of disease processes and as such, may examine the relationship between specific diseases and IP differently to conventional medicine [20,21]. The clinical experience of CIM practitioners may be drawn upon to further examine the relationship between IP and disease. Through application of a robust HSR framework and employment of HSR methods such as surveys and Delphi studies, CIM practitioners' clinical experience may be captured and provide insights to diseases observed to be associated with IP, yet remain unrecognised in the current empirical literature. This new knowledge may lay the foundations to advancing clinical and epidemiological research for the disease in question. There may also be value in exploring the degree to which CIM practitioners have experienced a reduction in their patients' clinical symptoms by treating IP. Moreover, potential risk factors or other factors associated with the onset and exacerbation of IP as observed by CIM practitioners in clinical practice may be identified through HSR and later verified by future empirical research. For these reasons alone, mapping the CIM practitioners' clinical perspective of the correlation between IP and disease may assist not only CIM research but also the wider health research community.

#### 4.2. Advancing approaches to diagnosis and testing

CIM practitioners from CIM professions such as naturopathy focus on gastrointestinal function (and dysfunction) as a major principle of disease management and are known to use an array of methods to investigate digestive health [20,21]. Little is currently known regarding the testing methods utilised by CIM practitioners to measure IP in clinical practice. However, the dual sugar and serum zonulin tests are fast becoming accepted as the most effective assessment tools for measuring IP [26]. Exploring the methods used by CIM practitioners to assess IP using a HSR model may provide a useful foundation for future clinical research. For example, exploring the frequency in which serum zonulin is used in clinical practice to what treatment methods are employed may expand the use of zonulin as a biomarker. Research questions worth investigating include, are CIM practitioners employing different methods to measure IP? At what point during patient care do CIM practitioners test for IP? What factors influence CIM practitioners to test or not test IP in their patients? Once answers to these questions are known, they can be checked against best practice and provide an opportunity to better inform CIM practitioners to test appropriately. Furthermore, understanding the signs and symptoms CIM practitioners associated with a positive IP test through the use of vigorous survey research may form the basis for the development of a validated diagnostic instrument. Investigating CIM practitioners' methods of testing IP may provide an opportunity to understand what CIM practitioners have found to be useful and advance the diagnostic criteria.

#### 4.3. New possibilities for treatment and management

Through deductive reasoning, CIM practitioners may have identified potentially useful treatments from existing literature and traditional knowledge and applied these treatments with varying success in clinical practice [22]. There are a number of therapeutic agents that have been suggested to support the management of IP. These include vitamin D [45], quercetin [46] and zinc [47] and they have been suggested to directly act upon the TJ to modulate IP. Furthermore, therapeutic agents that modulate risk factors of IP such as dysbiosis and inflammation have the potential to influence IP indirectly and include *Curcuma longa* [48], probiotics [33], *Saccharomyces boulardii* [49] and particular strains of probiotics such as *Lactobacillus rhamnosus GG* [50,51]. Concurrent therapeutic agents that modulate IP directly and indirectly may potentially have a synergistic effect within a whole system treatment approach. Employing HSR to investigate treatment

approaches that are successfully employed by CIM practitioners may indicate a useful avenue for future exploration by clinical researchers. Research questions that may be answered through this approach include, have CIM practitioners observed clinical effects for any of these individual treatments? Have CIM practitioners observed other potential combinations or synergistic effects within their clinical practice? Furthermore, are there treatments that CIM practitioners employ and observe to be clinically beneficial which are not currently being explored in clinical research and warrant research attention? This information can be obtained through a HSR model utilising self-administered surveys or collating case studies implemented by CIM practitioners. Investigating the treatment methods used by CIM practitioners may act as a practice guide and open up new areas for research. Furthermore, surveying CIM practitioners on the period of time required to correct IP may indicate the ideal time frame to conduct new therapeutic intervention studies.

## 5. Conclusion

Utilising HSR as a means of investigating clinical practice may identify new knowledge that may translate to improvement in patient care and give direction for future WSR. The theory presented in this paper provides and emphasises the value of clinical insights and experience to the advancement of health research. As such, the approach to research proposed here has relevance to clinicians by actively including them in the research developments affecting their practice. It also has potential value for both CIM and conventional medicine researchers interested in supporting clinically relevant research. Investigating CIM practitioners within clinical practice may provide advancements in the clinical understanding of IP and other such health conditions, resulting in the improvement of patient centred care.

## Conflict of interest

All authors declare that there are no conflicts of interest regarding the publication of this paper.

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