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Integrating Complementary and Alternative Medicine into Family Medicine Practice: Narrative Review

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Abstract

Complementary and Alternative Medicine (CAM) has witnessed a significant surge in usage across various populations and regions in recent decades. This review article delves into the prevalence and patterns of CAM usage, from cancer patients to cultural practices in Saudi Arabia and New Zealand. In Saudi Arabia, CAM practices, especially spiritual ones like prayer and reciting the Quran, are widely adopted, with herbs, honey, and dietary products also being popular. New Zealand healthcare professionals, including general practitioners and midwives, generally hold a positive view towards CAM, with acupuncture being particularly favored. However, concerns about CAM's scientific evidence, safety, and costs persist. In the U.S., while CAM is popular, many family physicians feel inadequately trained to address CAM-related patient queries. In Germany, a significant number of family physicians use CAM in their practices, emphasizing the need for increased CAM education and research. The data underscores the global trend of CAM adoption and the need for its effective integration into mainstream healthcare. Despite its popularity, the integration of CAM in medical education remains limited in many regions, including Saudi Arabia. However, there's a noticeable shift with some medical schools beginning to incorporate CAM into their curriculum. The article underscores the importance of evidence-based practice, education, training, open communication, regulation, interdisciplinary collaboration, a patientcentered approach, thorough documentation, continuous research, cultural sensitivity, and cost-effectiveness evaluation when considering the integration of CAM into mainstream healthcare. The recommendations provided aim to ensure that patients receive holistic care that is both safe and effective. The

	overarching theme is the need for a balanced, informed, and collaborative approach to integrating CAM into family medicine practice.
CC License CC-BY-NC-SA 4.0	Keywords: Complementary Medicine, Alternative Medicine, Family Medicine, General Practice

Introduction:

Complementary and alternative medicine (CAM) encompasses a diverse range of health practices, systems, and products that are not generally considered part of conventional medicine [1]. Over the past few decades, there has been a growing interest in CAM, with surveys indicating that a significant proportion of the population in many countries have used at least one form of CAM [2]. This surge in popularity can be attributed to various factors, including dissatisfaction with conventional treatments, cultural beliefs, and the desire for a more holistic approach to health [3].

Family medicine, being the cornerstone of primary care, is often the first point of contact for patients seeking health advice and treatment. Given the increasing demand for CAM, family physicians are frequently confronted with questions regarding the safety, efficacy, and integration of these therapies into conventional treatment regimens [4]. This necessitates a comprehensive understanding of CAM modalities, their evidence base, and their potential interactions with standard medical treatments.

Historically, the relationship between conventional medicine and CAM has been characterized by skepticism and, at times, outright dismissal. However, the landscape is changing. A growing body of research is shedding light on the potential benefits of certain CAM modalities, prompting a shift towards a more integrative approach in healthcare [5]. This approach, known as Integrative Medicine (IM), seeks to combine the best of conventional and alternative therapies based on evidence, ensuring safety and efficacy [6].

With a rising trend of cancer patients turning to integrative therapies, it's crucial for doctors to guide them effectively through these treatments. Yet, even with its growing appeal to patients, integrative medicine hasn't been widely embraced within the conventional healthcare framework. This hesitation can be attributed to several factors: clinicians might not be fully aware of research and trials that prove the effectiveness of these therapies, challenges in covering the costs of such treatments, and a limited availability of resources to help healthcare professionals locate integrative medicine experts and materials. [7]

In a study aimed to identify the extent to which the elderly use complementary and alternative medicine (CAM), folk medicine, and other unconventional therapies. The findings indicate that older adults often use folk medicine and CAM for self-care, combining them with traditional medical treatments. While the decision to use these alternative therapies is common across different cultures, the specific treatments chosen are usually influenced by an individual's cultural or ethnic background. Many conventional healthcare providers might be unaware of this trend among the elderly. Case managers, who oversee elderly care transitions and promote health, can play a pivotal role in supporting and enhancing the integration of both traditional and non-traditional medical practices for the elderly [8]

Complementary and alternative medicine (CAM) is frequently used by adults diagnosed with cancer, with recent data indicating that as many as 87% of cancer patients employ at least one CAM method post-diagnosis. The National Institutes of Health's National Center for Complementary and Integrative Health differentiates between complementary therapies, which are non-traditional practices used alongside standard medicine, and integrative medicine, which merges evidence-based mainstream and complementary treatments in a holistic manner, addressing the entire individual rather than just a specific ailment or body part. On the other hand, alternative therapies replace standard treatments, a method that lacks evidence backing and is infrequently adopted by cancer patients. CAM covers a broad spectrum of treatments, such as biologically-based treatments like vitamins and herbs; mind-body practices like yoga and meditation; physical manipulations like massage and chiropractic care; energy-based methods like reiki; alternative medicinal systems like naturopathy; and lifestyle-based approaches involving diet and exercise. [9]

The integration of CAM into family medicine is not without challenges. The vastness of CAM modalities, ranging from acupuncture and herbal medicine to mind-body practices, means that family physicians must be equipped with knowledge that extends beyond the realms of conventional medicine [10]. Moreover, the evidence base for CAM is varied, with some therapies having robust supporting evidence, while others remain largely untested [11].

Many cancer patients use CAM, but they often don't discuss it with their oncology healthcare professionals, with up to 77% choosing not to disclose their use. Patients commonly refrain from discussing CAM because they feel their healthcare provider might be indifferent or even against it, they think CAM doesn't impact their standard cancer treatment, or simply because the topic wasn't brought up by the provider. Some patients might not even recognize what they're using as CAM, assume that natural products won't interfere with prescribed medications, feel that their healthcare provider lacks knowledge about CAM, or doubt the depth of their provider's understanding of CAM. On the healthcare provider's side, the primary reasons for not discussing CAM are typically a lack of knowledge and comfort in addressing the topic. This communication gap means healthcare providers might miss crucial chances to discuss the potential advantages and disadvantages of CAM with their patients. [9.2]

In Saudi Arabia, CAM practices often stem from the religious convictions of its users. Commonly adopted methods include Holy Quran therapy, the use of honey, black seed, and myrrh, as well as Alhijama (cupping), which is considered a part of prophetic medicine. More contemporary treatments, such as acupuncture, have also been introduced to the Saudi community, primarily through established clinics, with the private sector being the main proponent of such practices. [12]

This review aims to provide family physicians with an evidence-based overview of the most commonly used CAM modalities, offering insights into their potential benefits, risks, and considerations for integration into family medicine practice. As the healthcare paradigm shifts towards a more patient-centered and holistic approach, it is imperative for family physicians to be at the forefront of this change, guiding their patients with informed and balanced advice [13].

Extent of Usage of Complementary and Alternative Medicine (CAM)

Complementary and Alternative Medicine (CAM) encompasses a broad range of practices that are not part of mainstream medicine but are used alongside or in place of conventional treatments. Over the past few decades, the use of CAM has seen a significant rise across various populations and regions.

The extent to which integrative medicine is used can differ widely among studies, but comprehensive reviews indicate that about a third to half of cancer patients employ some kind of integrative treatment. When looking at head and neck cancer specifically, the usage rates can vary even more, from as low as 6% to as high as 79%. This discrepancy might be due to how the data is collected or when it's gathered. It's worth noting that the use of integrative medicine among head and neck cancer patients might see a significant rise after they've been diagnosed and started their treatment. [7, 14, 15]

In a study aimed to offer an updated insight into the utilization of Complementary and Alternative Medicine (CAM) in Saudi Arabia, taking into account the cultural, religious, and psychosocial influences on health choices. The research revealed varied patterns of CAM usage. Spiritual practices, such as prayer and reciting the Quran, were predominant. Other CAM methods included the use of herbs (8–76%), honey (14–73%), and dietary products (6–82%). Cupping (Alhijamah) had a usage rate of 4–45%, and acupuncture was primarily practiced by professionals. In conclusion, CAM sees extensive use in Saudi Arabia. There's a pressing need for more focused research in this area and to enhance public awareness regarding the diverse CAM practices, with the national center of CAM expected to lead these initiatives. [12]

In a review explored the practices, attitudes, and knowledge of New Zealand healthcare professionals concerning complementary and alternative medicine (CAM). The research involved 2060 professionals like general practitioners (GPs), nurses, and midwives, among others. The findings revealed a generally positive stance towards CAM, though concerns about its scientific evidence, regulation, safety, and costs were evident. Approximately 25% of GPs practiced CAM, with 82.3% referring patients to CAM specialists. Among physiotherapists treating pregnant women, 48.4% used acupuncture, while 37.3% of midwives recommended CAM. Acupuncture was deemed the most beneficial CAM modality by GPs. Additionally, up to 58% of GPs and Plunket nurses expressed interest in further CAM education, and 66.7% of GPs believed CAM should be part of medical curriculums. [16]

In Saudi Arabia, another review highlighted that among Saudis, religious practices are the most common form of complementary and alternative medicine (CAM). This trend is also prevalent among citizens of the Middle East. Practices such as reciting the Quran, supplication, drinking Zamzam water or water blessed with Quranic verses, and using black seeds are popular. In a study conducted in Riyadh focusing on oncology patients, these

methods were the most frequently used. However, only a small percentage (7.4%) believed that CAM solely contributed to their health improvement. Globally, spiritual and religious CAM methods are also practiced, though the specifics vary based on factors like religion, age, gender, education, and the nature of the illness. While the actual effectiveness of these practices remains uncertain, many choose them because they believe in their health benefits, cost-effectiveness, accessibility, and potential to enhance the quality of life. It's also been observed that healthcare professionals generally have a decent understanding and positive view of these practices. In a study from Trinidad and Tobago, while many healthcare workers had a fair understanding of spiritual or religious CAM, only half discussed it with their patients, and a mere 15% would consider referring their patients to CAM specialists. However, many of these professionals believed that a combination of CAM and traditional medicine could be more beneficial than just traditional medicine. [17-21]

In the U.S., CAM is a popular choice among the public, with estimated out-of-pocket expenses reaching around \$27 billion. The medical community's acceptance of CAM has also seen an uptick in recent times. However, a significant portion of U.S. family physicians lack formal training in CAM. In a survey, while 76% of family physicians acknowledged their patients' use of CAM, a vast majority (84%) felt the need for more knowledge on the subject to address patient queries effectively. Recognizing this gap, the Group on Alternative Medicine of the Society of Teachers of Family Medicine introduced curriculum guidelines for CAM training during residency. Consequently, some family medicine residency programs have started incorporating CAM into their curriculum, supported by the National Center for Complementary and Alternative Medicine in the U.S. [22] An older study from 1998 indicated that in the USA, the adoption of alternative medicine was increasing from 33.8% in 1990 to 42.1% in 1997. In 2002, the most prevalent alternative therapies in the USA were prayer (45.2%), herbal remedies (18.9%), breathing-focused meditation (11.6%), general meditation (7.6%), chiropractic care (7.5%), yoga (5.1%), body treatments (5.0%), diet-centric therapy (3.5%), progressive relaxation techniques (3.0%), high-dose vitamin therapy (2.8%), and visualization practices (2.1%). [23]

In Germany, over two-thirds of patients utilize complementary and alternative medicine (CAM), offered by both physicians and non-medical practitioners known as "Heilpraktiker." A study aimed to determine the extent of CAM usage and attitudes among family physicians (FPs) in Germany. In total, 60% (886 out of 1,471) of the responding FPs indicated they use CAM in their practices. Among them, 55% (503 FPs) held a positive view of CAM, while 14% (127 FPs) had a somewhat negative perspective. The therapies deemed most beneficial by FPs were chirotherapy, relaxation, and neural therapy. The most frequently used CAM therapies in German family practices were neural therapy, phytotherapy, and acupuncture. The findings highlight the significant role CAM plays in primary care in Germany, suggesting a need for increased CAM education and research. The prevalent use of CAM by FPs also raises questions about the role of non-medical CAM practitioners in the German healthcare system. [22]

Recommendations for Integrating CAM into Mainstream Healthcare:

The integration of Complementary and Alternative Medicine (CAM) into mainstream healthcare has been a topic of interest and debate for many years. As the demand for CAM therapies continues to grow, it becomes imperative for healthcare systems to consider its integration to ensure patient safety, satisfaction, and holistic care. Here are some recommendations for integrating CAM;

Evidence-Based Practice: Before integrating any CAM therapy, it's essential to ensure that the practice is evidence-based. Rigorous scientific research should back the efficacy and safety of the therapy. Randomized controlled trials, systematic reviews, and meta-analyses should be consulted to determine the validity of the CAM therapy [23].

Education and Training: Healthcare professionals should receive adequate training and education about CAM therapies. This training will ensure that they can provide accurate information to patients, understand potential interactions with conventional treatments, and make informed recommendations [24].

While there's a global interest in CAM, its presence in medical education in Saudi Arabia is limited, and this trend is also observed in many developed nations. However, there are positive shifts in some Saudi medical schools as they begin to introduce CAM courses and integrate them into their curricula. Furthermore, medical students in the country believe that CAM should be a part of their studies. In a related study, nearly half of the surveyed students expressed satisfaction with their CAM education. [25]

Open Communication: Encourage patients to discuss their use or interest in CAM therapies. Open dialogue ensures that patients don't hide their CAM usage, which can lead to potential interactions or adverse effects [26].

A significant number of cancer patients might not fully understand their standard cancer treatments. Before diving into discussions about CAM, it's essential to ensure they have a clear grasp of their primary treatment. This can be achieved by using straightforward language and pointing them to educational materials. By doing so, it can enhance their comprehension, foster open dialogues about treatment options, and potentially shape their views and choices concerning CAM. [9]

Regulation and Licensing: Just like conventional medical practices, CAM practitioners should be regulated and licensed. This regulation ensures that only qualified individuals provide CAM therapies, ensuring patient safety [27].

When it comes to understanding CAM therapies, there's often confusion about their effectiveness and safety, especially concerning cancer. Helping cancer patients and their families access trustworthy information about CAM is crucial for making informed treatment choices that prioritize benefits and minimize risks. There are many reliable resources available that guide individuals on making educated decisions about CAM during their cancer journey and offer in-depth details about prevalent CAM treatments. For instance, comprehensive therapy guides can be shared in hectic clinical environments to address frequent queries among certain patient groups. [9]

Interdisciplinary Collaboration: Foster collaboration between conventional medical practitioners and CAM therapists. Such collaboration can lead to a more holistic approach to patient care, ensuring that all aspects of a patient's health are considered [28]

It's crucial to foster better understanding, dialogue, and collaboration between traditional and CAM professionals. Building strong inter-professional ties requires a foundation of comprehensive medical education and credentials. Beyond the specific CAM training for traditional healthcare providers, it's vital to offer structured medical education to CAM practitioners. This can ensure that they can converse using standard medical terminology and can correctly identify and diagnose severe conditions, addressing some of the primary concerns raised by general practitioners and pharmacists.[16]

Patient-Centered Approach: Always consider the patient's beliefs, values, and preferences when discussing or recommending CAM therapies. A patient-centered approach ensures that the care provided aligns with the patient's values and beliefs [29].

Documentation: Ensure that all CAM therapies used by a patient are documented in their medical records. This documentation ensures continuity of care and can be crucial in understanding potential interactions or side effects.

Research and Development: Encourage further research into CAM therapies. More research will lead to a better understanding of the efficacy, safety, and best practices associated with CAM [30].

Cultural Sensitivity: Recognize that many CAM therapies are rooted in specific cultural or traditional practices. Healthcare professionals should approach CAM with cultural sensitivity and respect [31].

Cost-Effectiveness: Evaluate the cost-effectiveness of CAM therapies. Integrating cost-effective CAM therapies can lead to better patient outcomes and potential cost savings for the healthcare system [32].

Conclusion:

The integration of CAM into mainstream healthcare requires a thoughtful and evidence-based approach. By considering the above recommendations, healthcare systems can ensure that patients receive safe, effective, and holistic care. More comprehensive research is mandatory in this important issue.

References:

1. National Center for Complementary and Integrative Health (NCCIH). (2018). Complementary, Alternative, or Integrative Health: What's In a Name? U.S. Department of Health & Human Services. https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name

- 2. Clarke, T. C., Black, L. I., Stussman, B. J., Barnes, P. M., & Nahin, R. L. (2015). Trends in the use of complementary health approaches among adults: United States, 2002-2012. National health statistics reports, (79), 1–16.
- 3. Astin, J.A. (1998). Why patients use alternative medicine: results of a national study. JAMA, 279(19), 1548-1553.
- 4. Kemper, K.J., Amata-Kynvi, A., Dvorkin, L., Whelan, J.S., Woolf, A., Samuels, R.C., & Hibberd, P. (2000). Herbs and other dietary supplements: healthcare professionals' knowledge, attitudes, and practices. Alternative therapies in health and medicine, 6(3), 58.
- 5. Vohra, S., Feldman, K., Johnston, B., Waters, K., & Boon, H. (2005). Integrating complementary and alternative medicine into academic medical centers: experience and perceptions of nine leading centers in North America. BMC Health Services Research, 5(1), 78.
- 6. Maizes, V., Rakel, D., & Niemiec, C. (2009). Integrative medicine and patient-centered care. Explore, 5(5), 277-289.
- 7. Matovina, C., Birkeland, A. C., Zick, S., & Shuman, A. G. (2017). Integrative Medicine in Head and Neck Cancer. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery, 156(2), 228–237. https://doi.org/10.1177/0194599816671885
- 9. Balneaves, L. G., Watling, C. Z., Hayward, E. N., Ross, B., Taylor-Brown, J., Porcino, A., & Truant, T. L. O. (2022). Addressing Complementary and Alternative Medicine Use Among Individuals With Cancer: An Integrative Review and Clinical Practice Guideline. Journal of the National Cancer Institute, 114(1), 25–37. https://doi.org/10.1093/jnci/djab048
- 10. Kligler, B., Maizes, V., Schachter, S., Park, C.M., Gaudet, T., Benn, R., Lee, R., & Remen, R.N. (2004). Core competencies in integrative medicine for medical school curricula: a proposal. Academic Medicine, 79(6), 521-531. [7]
- 11. Ernst, E. (2000). The role of complementary and alternative medicine. BMJ, 321(7269), 1133-1135.
- 12. Alrowais, N. A., & Alyousefi, N. A. (2017). The prevalence extent of Complementary and Alternative Medicine (CAM) use among Saudis. Saudi pharmaceutical journal: SPJ: the official publication of the Saudi Pharmaceutical Society, 25(3), 306–318. https://doi.org/10.1016/j.jsps.2016.09.009
- 13. Horrigan, B., Lewis, S., Abrams, D., & Pechura, C. (2012). Integrative medicine in America—How integrative medicine is being practiced in clinical centers across the United States. The Bravewell Collaborative.
- 14. Ernst E, Cassileth BR. The prevalence of complementary/alternative medicine in cancer: a systematic review. Cancer. 1998;83(4):777–82. doi: 10.1002/(SICI)1097-0142(19980815)83:4<777::AID-CNCR22>3.0.CO;2-O.
- 15. Horneber M, Bueschel G, Dennert G, Less D, Ritter E, Zwahlen M. How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysis. Integr Cancer Ther. 2012;11(3):187–203. doi: 10.1177/1534735411423920
- Liu, L., Tang, Y., Baxter, G. D., Yin, H., & Tumilty, S. (2021). Complementary and alternative medicine

 practice, attitudes, and knowledge among healthcare professionals in New Zealand: an integrative review. BMC complementary medicine and therapies, 21(1), 63. https://doi.org/10.1186/s12906-021-03235-z
- 17. Aizuddin, A. N., Zamzuri, M. I. A., Mansor, J., Nurumal, S. R., Yunus, S. Z. S. A., Razak, M. A. A., Jamhari, M. N., Fah, T. S., Miskam, H. M., Hod, R., & Yusoff, H. M. (2022). Perception of integrating complementary and alternative medicine practice in patient's treatment among the healthcare practitioners: a systematic review. The Pan African medical journal, 43, 19. https://doi.org/10.11604/pamj.2022.43.19.31133
- 18. Alrowais NA, Alyousefi NA. The prevalence extent of Complementary and Alternative Medicine (CAM) use among Saudis. Saudi Pharm J. 2017;25(3):306–18
- 19. Abuelgasim KA, Alsharhan Y, Alenzi T, Alhazzani A, Ali YZ, Jazieh AR. The use of complementary and alternative medicine by patients with cancer: a cross-sectional survey in Saudi Arabia. BMC Complement Altern Med. 2018 Mar;18(1):88.
- 20. Qureshi NA, Khalil AA, Alsanad SM. Spiritual and Religious Healing Practices: Some Reflections from Saudi National Center for Complementary and Alternative Medicine, Riyadh. J Relig Health. 2020;59(2):845–69.

- 21. Bahall M, Legall G. Knowledge, attitudes, and practices among health care providers regarding complementary and alternative medicine in Trinidad and Tobago. BMC Complement Altern Med. 2017;17(1):1–9
- 22. Joos, S., Musselmann, B., & Szecsenyi, J. (2011). Integration of complementary and alternative medicine into family practices in Germany: results of a national survey. Evidence-based complementary and alternative medicine: eCAM, 2011, 495813. https://doi.org/10.1093/ecam/nep019
- 23. Ernst, E., & Cohen, M. H. (2001). Informed consent in complementary and alternative medicine. Archives of Internal Medicine, 161(19), 2288-2292.
- 24. Kemper, K. J., Gardiner, P., & Gobble, J. (2006). Expertise about herbs and dietary supplements among diverse health professionals. BMC Complementary and Alternative Medicine, 6(1), 15
- 25. Al Mansour M.A., Mohammad E.Y., Abdalla S., Medani K., Mahmoud W., Meraj S. Satisfaction, self-use and perception of medical students in Majmaah University, Kingdom of Saudi Arabia, towards complementary and alternative medicine. J. Taibah Univ. Med. Sci. 2015;10(1):74–78
- 26. Adams, K. E., Cohen, M. H., Eisenberg, D., & Jonsen, A. R. (2002). Ethical considerations of complementary and alternative medical therapies in conventional medical settings. Annals of Internal Medicine, 137(8), 660-664.
- 27. Cohen, M. H., & Eisenberg, D. M. (2002). Potential physician malpractice liability associated with complementary and integrative medical therapies. Annals of Internal Medicine, 136(8), 596-603.
- 28. Boon, H., Verhoef, M., O'Hara, D., & Findlay, B. (2004). From parallel practice to integrative health care: a conceptual framework. BMC Health Services Research, 4(1), 15.
- 29. Epstein, R. M., & Street, R. L. (2011). The values and value of patient-centered care. Annals of Family Medicine, 9(2), 100-103.
- 30. Wieland, L. S., Manheimer, E., & Berman, B. M. (2011). Development and classification of an operational definition of complementary and alternative medicine for the Cochrane collaboration. Alternative Therapies in Health and Medicine, 17(2), 50.
- 31. Napier, A. D., Ancarno, C., Butler, B., Calabrese, J., Chater, A., Chatterjee, H., ... & Guesnet, F. (2014). Culture and health. The Lancet, 384(9954), 1607-1639.
- 32. Herman, P. M., Poindexter, B. L., Witt, C. M., & Eisenberg, D. M. (2012). Are complementary therapies and integrative care cost-effective? A systematic review of economic evaluations. BMJ Open, 2(5), e001046.