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SCOPING REVIEW ARTICLE
IN INTEGRATED MEDICINE

A scoping review examining the relationship between green tea and skin cancers

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Abstract

Introduction: Skin cancers are among the most commonly diagnosed cancers in the US and are becoming a major public health problem. Polyphenols particularly, (-)-epigallocatechin-3-gallate (EGCG) found in green tea has been shown to have anti-carcinogenic properties in animal models. Chemo-preventative role of green tea has been studied through epidemiological studies in several cancers such as breast, lung, oral cavity and others. The results have been mixed.
Purpose: The purpose of this study was to conduct a scoping review to examine the relationship between green tea and skin cancers and discuss its implications for humans.
Methods: Literature searches using the keywords "green tea" and skin cancer" were conducted in MEDLINE (PubMed), CINAHL, and Google Scholar. The inclusion criteria were: (1) articles published in the past approximately ten years; (2) in the English language; (3) published in peer-reviewed journals in the above databases; and (4) all accounts of descriptive and epidemiological or evaluation studies. Excluded were articles published before 2008, published in grey literature and non-peer-reviewed journals.
Results: In the literature, systemic and topical applications of green tea polyphenols have shown to have mixed effects against the formation and development of skin cancers in animals. Particularly, EGCG has been found as a contributing factor to inhibit cell invasion, angiogenesis, and metastasis in skin cancer.
Discussion: Use of green tea and its extracts may offer promising implications for use in humans about prevention and retarding the progress of skin cancers but at present, the data are very limited. Large scale randomized controlled trials on the efficacy of green tea and its extracts are required.

KEY WORDS: Green tea; melanoma; non-melanoma skin cancer; review; skin cancer.

Riassunto

Introduzione: Questa è uno studio sugli effetti diretti e indiretti delle esperienze di discriminazione sull'utilizzo dell'assistenza sanitaria tra i giovani studenti universitari.
Metodi: Centottantacinque studenti hanno completato un'indagine online. Le misure includevano esperienze di discriminazione, aspettative di risultato, autoefficacia, atteggiamenti e variabili demografiche. Le relazioni testate sono state informate dal modello comportamentale di Andersen sull'uso dei servizi sanitari, che è stato modificato in quanto semplifica eccessivamente il ruolo dell'etnia considerata come predittore. Sono state condotte analisi di regressione e di mediazione.
Risultati: L'autoefficacia nel comunicare con i medici è stata un fattore predittivo diretto significativo dell'utilizzo dell'assistenza sanitaria (t = 2.965, P = .003), sebbene le esperienze di discriminazione non lo fossero. È stato inoltre riscontrato che gli effetti della discriminazione sull'utilizzo dell'assistenza sanitaria sono mediati dall'autoefficacia per comunicare con i medici (95% CI [-.0907, -.0025]).
Conclusioni: Questi risultati hanno fornito supporto per l'inclusione delle variabili psicosociali (ovvero l'autoefficacia) nel modello di Andersen per aumentare il suo potere esplicativo.

TAKE-HOME MESSAGE

The findings of this literature review suggest that green tea consumption and topical application may be helpful in lowering skin cancer in humans.

Competing interests - none declared.

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INTRODUCTION

Skin cancer is considered a significant public health issue. Skin cancer rates have doubled in the USA from 1982 to 2011 [1, 2]. Worldwide, the rates of skin cancers have been on an inclining trend [3]. Non-melanoma skin cancers, including basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), were found to be the most commonly diagnosed of all forms of cancer, with over 3 million Americans diagnosed each year. Both types of skin cancers are found to be treatable if detected early. Melanoma, the most fatal form of skin cancer, is less common but responsible for the majority of skin cancer deaths. The American Cancer Society has estimated that in the United States in 2019 roughly 96,480 new melanomas cases will be diagnosed in 2019 and roughly 7,230 people will die of melanoma [5].

Green tea has been considered a health beneficiary beverage. Leaves and buds of *Camellia sinensis* plant which have not undergone a withering and oxidation process are considered as green tea. Literature has shown multiple health benefits of green tea. Its use in both forms, oral consumption and topical applications, has been reported beneficial in skin conditions. Green tea polyphenols (GTPs) and Catechin are two naturally available elements in green tea that have been studied for their effects on multiple diseases. Green tea usages in drinking and topical form have been reported to be beneficial in protecting skin from skin cancer. Its polyphenols protect skin from several damaging effects of UV-induced sunburn response, UV-induced immunosuppression, and photoaging [6]. Polyphenols exhibit their photoprotective effect by various cellular, molecular, and biochemical mechanisms in *vitro* and in *vivo* system [6]. In a review of animal-based laboratory studies, green tea polyphenols were found effective in protecting skin from ultra-violet radiation-induced inflammation and in DNA damage [7]. In another review, it was found that GTPs in drinking water as well as in the topical application of (-)-epigallocatechin-3-gallate (EGCG) acts in a variety of ways and prevent UVB-induced skin tumor development in mice. Mainly six mechanisms which are regulated by GTPs and EGCG at the molecular level play an important role in the prevention of skin cancer. Katiyar et al (2007) have reported in their review that these chemicals present in green tea protect and prevent skin cancer by initiating immunoregulatory cytokine interleukin (IL) 12; IL-12-dependent DNA repair following nucleotide excision repair mechanism; inhibition of UV-induced immunosuppression through IL-12-dependent DNA repair; inhibition of angiogenic factors; and stimulation of cytotoxic T cells in a tumor microenvironment [8]. Similarly, several pathways of GTPs, EGCG in inhibiting skin cancer were reported in animal and human cell studies [9]. Butt and Sultan have reported that GTPs of green tea have chemoprophylactic properties which are claimed to have the potential to work against several forms of cancer [10]. Laboratory studies conducted on mice have been found to be somewhat promising in demonstrating a preventive effect on skin cancers [11]. Consumption or topical use of green tea may similarly be useful in preventing skin cancer in humans. A catechin, gallic acid also known as epigallocatechin-3-gattate (EGCG), and polyphenols, theaflavins (TF), thearubigins (TR), epicatechin, epicatechin-3-gallate, and epigallocatechin have been studied for skin cancer [12].

Objective of the study

This study conducted a scoping review to examine the relationship between green tea and skin cancers and discuss its potential implications for humans.

METHODS

An extensive literature search was performed using the keywords "green tea" and "skin cancer" in the following databases: MEDLINE (PubMed), CINAHL, and Google Scholar. Studies with all methodological approaches conducted on animals and humans in the past approximately 10 years from 2008 to May 2019 were included. We customized our

search by selecting a year in all databases. We conducted the literature search in May 2019. We considered the following inclusion criteria: (1) articles published in the English language; (2) published in peer-reviewed journals; and (3) descriptive, epidemiological or evaluation studies. Articles published in other than the English language, published before 2008, review articles, non-empirical descriptive articles, and those not in peer-reviewed journals were excluded. Based on keywords, a total of 346 papers were found in the databases. We found 192 studies in MEDLINE (PubMed), 02 in CINAHL, and 152 in Google Scholar. After careful reading of titles and excluding papers which appeared in the databases in our search, 56 papers were found relevant and their abstracts were read. *In vitro* and *in vivo* laboratory studies in mice; *in silico*; *in vitro*, *in vivo,* mixed *in vitro* and *in vivo* with human cells; observational studies in humans including case-control and cohort; and double randomized studies with humans were included in the review. A total of 37 studies were deemed eligible to be included in our analysis (Figure 1). Descriptive analysis was performed to determine the distribution of studies selected.

RESULTS

Out of the total of 37 studies, 25 studies suggested some preventive or inhibitory role, two moderate to protective effect, and four contented that green tea may be effective in protecting against skin cancer. Looking at the difference between studies conducted on mice and humans, all studies in mice indicated either preventive or protective effect while in humans all laboratory and only one case-control study demonstrated preventive to a protective effect for skin cancer. Of the total number of studies included in this review, 24.02% studies conducted in mice, 40.0% in the laboratory, and 10.81% clinical and observational studies in humans have shown some preventive, protective, and inhibitory responses against the various forms of skin cancers. All studies conducted in mice, 100% showed preventive to protective effects while in humans 60% demonstrated such effects (Tables 1 and 2). Studies, included in this review are presented in a following sequence and chronological order: *in vitro* mice, *in vivo* mice, *in vitro* human, *in vivo* human, *in vitro and vivo* human, case-control, prospective cohort, and double blind randomized.

Out of total 37 studies, 16 were conducted in the United States, six in India, four in China, three in Japan and UK each, two in Australia, and one in each country including Switzerland, South Africa, and Germany. Total nine laboratory studies came from the United States, and one from each country including India, Japan, South Africa, and Germany. Regarding the mice models, five studies were found from India, two from United States, and one from China, and Australia. One study was *in silico* in humans [24], two *in vit*ro in mice [13, 14], eight *in vitro* in humans [25, 26, 27–32], nine *in vivo* in mice [15–23], five *in vivo* in humans [33–37], three mixed *in vitro* and *in vivo* in humans [38–40], two case-control [41, 42], four cohort [43–46], and three double-blind randomized control studies in humans [47–49] were found.

In the mice models, four studies demonstrated some preventive, protective, and inhibitory response of polyphenols through chemopreventive mechanism [16, 21, 23, 36], against UV-induced skin cancer [17–19, 22], and by inhibiting DNA damage [14, 35].

In the laboratory-based studies, protecting, preventive, and inhibiting response of polyphenols towards skin cancer was found through chemopreventive properties of GTPs in stimulating the cytotoxic T-cells in tumor microenvironment [24, 25, 27, 30, 32–34, 38–40], inhibition of UV-induced immunosuppression through IL-12-dependent DNA repair [35–38], and DNA repair through nucleotide excision repair mechanism [26, 28, 29].

In the observational studies, chemopreventive action was noted in seven studies [31, 41–46], and inhibition of UV-induced immunosuppression through IL-12-dependent DNA repair in three studies [44, 48, 49].

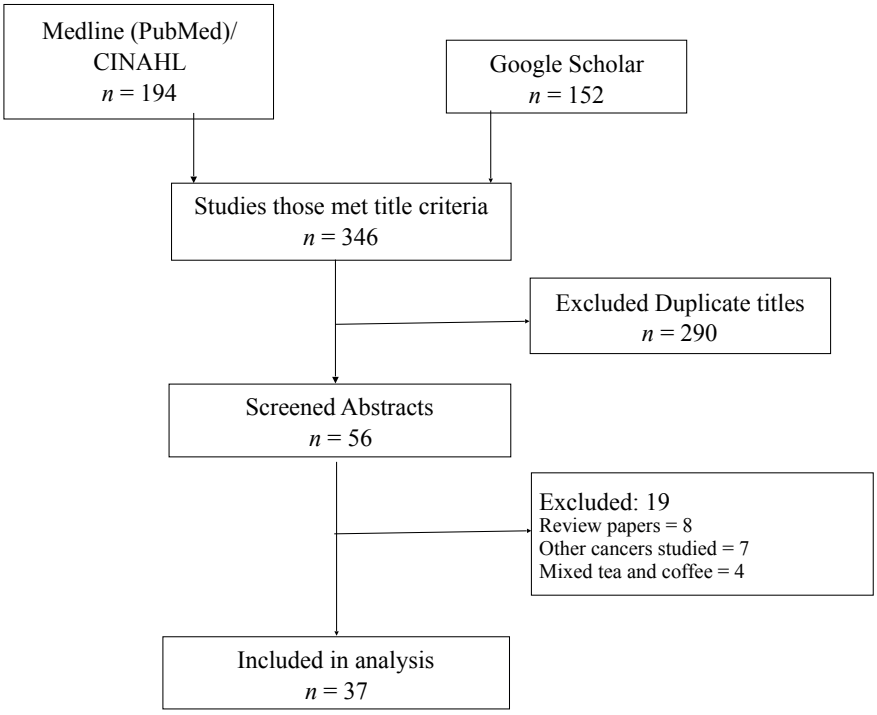

Figure 1. Flow diagram of the literature search process.

Table 1. Summary results of all studies in the review (*n* = 37).

Category	Study Types (*n* = 37)	Results				
		Preventive /inhibitory role	Moderate to mild protective effect	May be effective / protective	No effect	No conclusion
Mice model (n =11)	*In vitro (n = 2)*	1		1		
	In vivo (n = 9)	8		1		
Human studies (n =26)	*In silico (n = 1)*	1				
	In vitro (n = 8)	8				
	In vivo (n = 5)	1	1	2		1
	In vitro and in vivo mixed (n = 3)	2	1			
	Case-control (n = 2)		1		1	
	Prospective cohort (n = 4)	2			2	
	Double-blind randomized (n = 3)			1	2	
Total		**23 (62.2%)**	**3 (8.1%)**	**5 (13.5%)**	**5 (13.5%)**	**1 (2.7%)**

DISCUSSION

The purpose of this scoping review was to examine the relationship between green tea and its putative effects on the prevention of skin cancer. Overall, the review collectively demonstrated through analysis of various in-vitro, in-vivo laboratory studies in animal models and humans, observational studies (case-control and cohort) and double-blind randomized controlled trials that green tea elements, when consumed as a green tea extract (GTE) in combined form, may lead to some potential protective and preventive effects against skin cancer in humans [34, 38]. Results of this review are consistent that various Polyphenols available in green tea triggers several biochemical, photochemical [50], molecular [51], and epigenetic reaction [52] that inhibits, prevents, and protects skin cancer in mice and human [53]. There are several criteria for establishing causality [54].

Table 2. Reviewed studies and their salient findings (*n* = 37).

Authors	Country of study	Year	Study type	Outcome variables	Findings	Conclusion
A. In vitro Mice						
1. Liao et al. 2016 [13]	China	2016	In vitro Mice laboratory study	EGCG-nanoethosomes for human melanoma cells induced in mice	DT-EGCG-nanoethosomes exhibited a significant therapeutic effect, with tumors shrinking, on average, by 31.5% of initial volumes after 14 d treatment.	May have an inhibitory role
2. Chen et al. [14]	China	2018	In vitro Mice laboratory study	Relationship between tea polyphenol and Toll-like receptor 4 (TLR4)	Tea polyphenol (TP) may inhibit melanoma (B16F10) growth in vivo	May have a preventive role
B. In vivo Mice						
3. Patel et al. [15]	India	2008	In vivo Mice laboratory study	Antitumor promoting effects and mechanisms of polymeric black tea polyphenols (PBPs 1–5)	Mild protective effects	May have mild protective effects
4. Roy et al. 2009 [16]	India	2009	In vivo Mice laboratory study	7,12-dimethylbenz[a] anthracene (DMBA) polyphenol on tumorigenesis	May act as a chemopreventive agent against skin cancer.	May have a preventive role
5. Meeran et al. 2009 [17]	USA	2009	In vivo Mice laboratory study	Effect of polyphenols in drinking water on the molecular mechanism of the inhibitory role	Reduced UVB-induced tumor development	May have an inhibitory role
6. Katiyar et al. 2010 [18]	USA	2010	In vivo Mice laboratory study	Relationship between GTPs in drinking water (0.1-0.5%, w/v) with UV-induced immunosuppression effect	GTPs showed the property of reacting against photocarcinogenesis.	May have a preventive and an inhibitory
7. George et al. 2011 [19]	India	2011	In vivo Mice laboratory study	Chemopreventive effects of resveratrol and black tea polyphenol (BTP) in mouse skin carcinogenesis	Suppress cancer cells may be beneficial against cancer	May have a preventive and an inhibitory role
8. Kumar et al. 2012 [20]	India	2012	In vivo Mice laboratory study	Effect of Polymeric black tea polyphenols (PBPs) on tumor promoter 12-O-tetradecanoylphorbol -13-acetate (TPA)	Polymeric black tea polyphenols (PBPs) may possess mouse skin anti-tumor-promoting effects.	May have a preventive and an inhibitory role
9. Ireland et al. 2012 [21]	Australia	2012	In vivo Mice laboratory study	Anticancer effect of Melaleuca alternifolia (tea tree) oil (TTO)	Topical application showed anticancer effect on mice	May have a preventive and an inhibitory role
10. Conney et al. 2012 [22]	USA	2012	In vivo Mice laboratory study	Green tea relationship with ultraviolet B radiation (UVB)-induced skin carcinogenesis in SKH-1 mice.	Oral administration of green tea inhibits ultraviolet B radiation (UVB)-induced skin carcinogenesis in SKH-1 mice.	May have an inhibitory role
11. Subramanian et al. 2014 [23]	India	2014	In vivo Mice laboratory study	Effect of Gallic acid on skin cancer	Topical application of Gallic acid in green tea (GA) inhibited DMBA/ Croton oil-induced two-stage skin carcinogenesis in mice	May have an inhibitory role
C. In silico Humans						
12. Kuzuhara et al. 2008 [24]	Japan	2008	In Silico Human study	Cancer preventing mechanism of Catechin	Green tea Catechin may induce cancer-preventive activity	May have a preventive role

continued

Authors	Country of study	Year	Study type	Outcome variables	Findings	Conclusion
D. In vitro Human cells						
13. Halder et al. 2008 [25]	India	2008	In vitro Human Laboratory study	Anticancer effect of Thearubigins (TR) Polyphenols of black tea	Theaflavins (TF) and Thearubigins (TR) polyphenols of black tea may have preventive effect	May have a preventive effect
14. Balasubramanian et al. 2009 [26]	USA	2009	In vitro Human Laboratory study	Polyphenols influence in PcG-mediated epigenetic regulatory mechanism	Green tea polyphenols may reduce skin tumor cell survival	May have preventive role
15. Shen et al. 2009 [27]	China	2009	In vitro human laboratory study	Different doses of Epigallocatechin-3-gallate (EGCG) on melanoma cells	Tumor growth was inhibited	EGCG useful for TRAIL-based treatment for melanoma
16. Choudhury et al. 2011 [28]	USA	2011	In vitro Human laboratory study	Impact of (-)-epigallocatechin-3-gallate (EGCG) and 3-deazaneplanocin A (DZNep) on PcG proteins (Ezh2, eed, Suz12, Mel18 and Bmi-1)	Both EGCG and DZNep independently and in combination reduces PcG proteins which inhibits skin cancer	May have inhibitory role
17. Nandakumar et al. 2011 [29]	USA	2011	In vitro human laboratory study	Epigenetic mechanism of EGCG on cancer	Chemoprevention of skin cancer	May have preventive role
18. Singh and Katiyar, 2011 [30]	USA	2011	In vitro human laboratory study	Inhibiting role of EGCG on melanoma cell invasion/migration	Green tea Catechin can inhibit melanoma cell invasion/migration	May have inhibitory role
19. Prasad and Katiyar, 2015 [31]	USA	2015	In vitro human laboratory study	Effect of GTPs Epicatechin on Melanoma cancer cells	Polyphenols found to be playing preventive and suppressor role	May have a preventive and inhibitory role
20. Roomi, et al. 2017 [32]	USA	2017	In vitro human laboratory study	Matrix metalloproteinase (MMP)-2 and -9	MMP plays an inhibiting role in the management of melanoma.	May have inhibitory role
E. In vivo Humans						
21. James Morré et al. 2009 [33]	USA	2009	In vivo in Human topical use on cancer	Green tea concentrated patch	Apoptotic blisters formed	No conclusion
22. Mnich et al. 2009 [34]	Switzerland	2009	In vivo Human laboratory study	Low dose topical use of GTE (OM24®) on UVB-induced skin cancer	GTE was found to be photochemopreventive agents.	May have a preventive role
23. Zhu et al. 2014 [35]	China	2014	In vivo human laboratory study	Epigallocatechin-3-gallate (EGCG) and ionizing radiation	Epigallocatechin-3-gallate (EGCG) shown potential effect in inhibiting skin cancer cells in human in ionizing radiation-related skin cancer	May have an inhibitory role
24. Balasubramanian et al. 2015 [36]	USA	2015	In vivo human laboratory study	Relationship between (-) Epigallocatechin-3-gallate (EGCG) and Bmi-1	(-) Epigallocatechin-3-gallate (EGCG) reduces Bmi-1, Polycomb group (PcG) protein that has an epigenetic impact in inhibiting skin cancer.	May have an inhibitory role
25. Magcwebeba et al. 2016 [37]	South Africa	2016	In vivo human laboratory study	Ultraviolet B (UVB) radiation with intracellular interleukin-1α (icIL-1α)	Aqueous extracts of tea inhibit skin cancer by inhibiting UAB radiation with intracellular interleukin-1α (icIL-1α)	May have an inhibitory role
F. In vitro and in vivo mixed Humans						
26. Schwarz et al. 2008 [38]	Germany	2008	In vitro and vivo Human laboratory study	GTP effect through intracellular interleukin (IL-12) mediation on Ultraviolet B (UVB) radiation-induced skin cancer	Green tea extract (GTP) has protective effects	May have protective effects

continued

Authors	Country of study	Year	Study type	Outcome variables	Findings	Conclusion
27. Ellis et al. 2011 [39]	USA	2011	In vivo and in vitro mixed human laboratory study	The physiological effect of EGCG dose of (0.1–1 μM) on melanoma cell growth	Melanoma inhibition	May have an inhibitory role
28. Singh and Katiyar, 2013 [40]	USA	2013	In vivo and vitro mixed human laboratory study	Molecular mechanism of EGCG in inhibiting skin cancer by in inhibiting cAMP & PGE	Green tea had a mediating effect	May have an inhibitory role
G. Case-control Humans						
29. Asgari et al. 2011 [41]	USA	2011	Case-control study in human	Association between tea consumption and squamous cell carcinoma (SCC)	No effect on cutaneous squamous cell carcinoma (SCC)	No effect
30. Ferrucci et al. 2014 [42]	USA	2014	Case-control study in human	Association of tea with basal cell carcinoma	Suggested a modest protective effect. Caffeinated coffee plus tea was found to have modest protective effect on early-onset of basal cell carcinoma (BCC)	May have moderate protective effect
H. Prospective cohort Humans						
31. Fujiki et al. 2012 [43]	Japan	2012	Prospective cohort study in human	Green tea consumption on cancer	Delayed cancer	May have an inhibitory role
32. Miura et al. 2015 [44]	Australia	2015	Prospective cohort study in human	Association between black tea consumption and the incidence of basal cell and squamous cell carcinomas	Results did not support the hypothesis that high black tea consumption reduced risk of skin cancer	No effect
33. Fujiki et al. 2015 [45]	Japan	2015	Prospective cohort study in human	Different doses of EGCG on cancer tumor	May have preventive and anticancer effect	May have a preventive and an inhibitory role
34. Wu et al. 2015 [46]	USA	2015	Prospective cohort in human	Association of tea with lower risk of Melanoma	No effect on melanoma	No effect
I. Double-blind randomized Humans						
35. Farrar et al. 2015 [47]	UK	2015	Double blind randomized control trial in human	Impact of GTC on UVR induced inflammation	Oral GTC with vitamin C did not significantly reduce skin erythema, leukocyte infiltration, or eicosanoid	No effect
36. Clarke et al. 2016 [48]	UK	2016	Oral administration on human interventional study	Mechanism between Catechin and UVR	May have some preventive effect	May have a preventive effect
37. Farrar et al. 2018 [49]	UK	2018	Double-blind randomization	1080 mg GTC dose on ultraviolet radiation (UVR) induced cancer	Oral consumption of GTC had no effect on cancer	No effect

The first one is the consistency of evidence. Based on this review it was found that the results showed some promise but the evidence is not conclusive. More studies especially double-blind randomized controlled trials would need to be undertaken to derive such consistent evidence. The second criterion is that of the strength of association. This review did not conduct a meta-analysis because the outcome variables were multifarious and methodologies were different including animal models and human studies. As a result, conclusion on the strength of the association criterion could not be established through this review. When more human studies become available future reviews would have to undertake such inquiry. The third criterion is that of specificity. A specific element, green

tea polyphenols (GTP) was found somewhat effective in the prevention of skin cancer in mice [18, 20, 26], as well in human cells [20, 31], in the laboratory and clinical studies. At the molecular level, polyphenols act in decreasing levels of cyclins and cyclin-dependent kinases of G1 phase of the cell cycle. Which further regulates the level of tumor suppressor proteins (Cip1/WAF1/p21, p16 and p53) that may inhibit skin cancer [31]. Other elements of green tea, Theaflavins (TF) and Thearubigins (TR) [16], in human studies and Gallic Acid [23], and epigallocatechin-3-gattate (EGCG) [13, 55–57], in mice laboratory studies were found to have inhibitory roles in skin cancer. Future researchers will have to work at establishing more specific evidence in this regard. The fourth criterion of causality is that of biological gradient or dose-response relationship which again could not be established through this review. The fifth criterion is that of temporality. Once again for that double-blind randomized controlled trials would need to be undertaken. The sixth criterion of biological plausibility seems somewhat satisfied due to encouraging results from both mice and human studies and also comparative evidence from other conditions. The seventh criterion of coherence or the idea not conflicting with previous evidence also seems to have some support from this review. The eighth criterion of experimental evidence has some support based on some empirical data presented in this review but once again double-blind randomized controlled trials would need to be undertaken to build strong empirical evidence. The final criterion of analogy which implies that there should be known associations that are similar to the one being studied has some basis due to the role of green tea as an anti-inflammatory agent [58], on brain functioning [59], on skin photoaging [60].

Results of this review suggest that more than one element found in green tea may have a potential preventive, protective, and inhibitory role in skin cancer. Even topical application of these elements has shown some anti-cancer effects in mice [21]. However, it cannot be asserted that green tea consumption and its topical use yields similar results in humans as is more common in animal models of mice. A few studies have found no effect on skin cancer or could not reach any conclusive evidence further warranting more investigation in this area. Previous reviews have also shown mixed results of green tea use for preventing skin cancer in humans. Compared to mice, studies in humans are very limited with no double-blind randomized controlled trials. Findings of this scoping review suggest the need for more randomized controlled clinical studies in humans.

Limitations and strengths

This review has few limitations including that the search was conducted through only three databases. Other databases were not included. Articles published only in the English language were included while grey literature was not explored. There could be publication bias. Often studies with favorable results are published so this review may not be able to trace studies with a negative outcome. This review attempted to find similarities between *in silico* model in humans, *in vitro* studies in mice and in humans, *in vivo* studies in mice and in humans, *in vitro* and *in vivo* mixed studies in humans, case-control studies, cohort studies, and double-blind randomized trials. Comparison between mice models and human studies may be affected because of different methodologies followed in studies. Observational studies on animals were not found so outcome comparison between such studies with humans were not evaluated. Some strengths of this review can be considered as inclusion of peer-reviewed articles, mostly published in reputable science journals, studies with contextual rigorous methodologies, and studies conducted by dependable academic and research institutions.

In conclusion, this review points toward potential benefits of green tea consumption and topical application in lowering skin cancer in humans, but further double-blind randomized controlled trials in this area are suggested.

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