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Review Article

Inhibitory effects of citrus peel extract in the risk reduction of cancer – A systematic review

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ABSTRACT:

Background: The citrus peel extract is one of the excellent preventative measures in lowering the incidence cases of cancers since it is rich in flavonoid. **Aim:** The systematic review aims to evaluate the effectiveness of flavonoid-rich citrus peel extract in reducing the risk of cancers in general. **Materials and method:** According to PRISMA guidelines, this study investigated several electronic databases from the beginning to 2024, including PubMed, Elsevier Science Direct, Wiley Online Library, SpringerLink, and Medline. The clinical trials conducted on experimental animals using proper validation tools and standardization methods of measurement. Out of 129 articles, 5 Randomized Clinical Trials carried out on experimental animals utilizing appropriate validation instruments and standardized measurement techniques were included. Studies were assessed for its anti-inflammatory, antioxidant, and anticarcinogenic properties. Quality assessment was done using the Office of Health Assessment and Translation (OHAT) Scale. **Results:** Citrus peel extract has been demonstrated in studies to operate in both the priming and activation stages of animal models to suppress tumor development, reduce oxidative stress, drastically inhibit inflammatory enzymes, and serve as an anticancer promoter. **Conclusion:** More human trials are needed to illustrate the dose-response relationship, even though studies on animals have shown that flavonoids in citrus peel extract dramatically lower the incidence of cancer.

Keywords: Auraptene, Nobiletin, Flavanoids, Phytochemicals, Chemoprevention, Carcinogenesis.

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INTRODUCTION

According to the IARC report, there were 20 million new cases and 9.7 million deaths due to cancer in the year 2022 throughout the world [1]. A lack of access, resources, and facilities in the healthcare system causes cancer cases to spike in developing countries like India [2]. In 2050, cancer will account for nearly 35 million new cases worldwide, or almost one in six. Lung, Breast, Colon, Rectum, Prostate, and Stomach cancer are the most common types [3]. Tobacco use is the single leading cause of cancer death. It accounted for about one-fifth of all the cancer deaths in the Low and Middle-Income Countries (LMCs) in 2002 [4]. The three most common viruses that cause cancer are Helicobacter pylori, Hepatitis B, Hepatitis C, and Human Papilloma Virus. One of the main causes of stomach cancer, which is not very treatable, is H. pylori. In many parts of the world, the prevalence of stomach cancer and H. pylori has drastically decreased without specific therapies, which raises the prospect of creating interventions for areas where the incidence is not dropping [5].

The current treatment options include hormone therapy, immunotherapy, radiation therapy, chemotherapy, surgery, and stem cell transplantation; all of these procedures are quite expensive. Integrative medicine provides ozone therapy, acupuncture, and wellness therapies [6]. The major adverse effects of these treatment modalities include air embolism, cramping, and Herxheimer reaction [7]. The treatment with anti-sclerostin antibodies alongside chemotherapy, radiotherapy, stem cell transplants, blood transfusions, and steroids and bone destruction was reduced in cancers such as multiple myeloma by

decreasing osteoclastic activity and increasing osteoblastic activity. Still, it showed metastases in other cancer types [8]. The development of effective prevention strategies to curb cancer risk is thus imperative.

There is a correlation between diet and physical activity levels, and they seem to interact in intricate ways to either protect or increase the risk of cancer. Global Burden of Disease and Risk Factors made separate estimates for the three components, namely whole grains, fruits, and sodium, based on the best available quantitative evidence and focusing on low fruit and vegetable intake as the best established specific dietary factor [9]. Phytochemicals are bioactive compounds produced by plants, including carotenoids, polyphenols, flavanoids, and dietary fibers. Orange peel extract contains a variety of flavanoids, including polymethoxylated flavones (PMF), flavonols, C- or O-glycosylated flavones, O-glycosylated flavanones, and several additional phenolic acids, as well as their related derivatives. The flavonoids in orange peel extract have anti-inflammatory, anticarcinogenic, anti-atherosclerosis, and antioxidant properties [10]. Flavonoids have been shown to have a wide range of anticancer properties, including their ability to alter the activity of enzymes that scavenge reactive oxygen species (ROS), stop cell cycles, induce autophagy and apoptosis, and inhibit cancer cell proliferation and invasion [11]. Citrus peels have been shown to protect against many diseases due to the presence of hesperidin, the most abundant flavonoid. Citrus Aurantium, citrus sinensis, citrus unshiu, citrus mitis, citrus clementine, lemons, limes, and grapefruits are known to contain compounds that protect against hypertension, cancer, and inflammatory and chronic diseases [12]. These citrus co-products, such as essential oil, were extracted from the peels of three distinct citrus species: C. limonum, C. reticulata, and C. paradisi. Limonene is the predominant component for the three, accounting for percentages of 56.3%, 76.5%, and 71.7% for C. paradisi, C. reticulata, and C. limonum, respectively shown to anticarcinogenic properties against breast and colon cancers in pre-clinical models [13]. This systematic review aims to determine the effectiveness of citrus peel extract in the risk reduction of different cancer types.

MATERIALS AND METHODS

Information sources: According to PRISMA guidelines, the following electronic databases were searched by TK and SS from conception until 2024: PubMed, Elsevier Science Direct, Wiley Online Library, SpringerLink, and Medline.

Search category: Boolean operators were used in the search strategies for the following keyboard combinations “Citrus fruits” AND “Citrus peel extract” AND “Carcinogenesis” AND “Chemoprevention” AND “Cancer treatment” AND “Auraptene” AND “Flavanoids” AND “Nobiletin” AND “Phytochemicals”.

Inclusion criteria: The clinical trials conducted on experimental animals were administered orally, subcutaneously, and intraperitoneally using proper validation tools and standardization methods of measurement were scrutinized by SR and PD. Only full-text original research studies published in English and using appropriate statistical analysis were included. Exclusion criteria: Studies published in regional languages or languages other than English and studies that were deemed redundant or irrelevant.

The study list was compiled based on the eligibility criteria by authors RM and DM. Data extracted from all the studies include citations (authors/years), where the study was conducted, the study design, details on samples recruited, the intervention provided, and methods of measurement, as represented in Table 1, and the results and inference in Table 2. Quality assessment was done by LF and IN using the Office of Health Assessment and Translation (OHAT) scale [14].

RESULTS

Original articles from the inception to the present have been compiled for this study. Out of the 132 total publications, 74 full-text articles were assessed independently. After removing duplicate articles and those with basic abstracts, 5 papers that satisfied the inclusion criteria were included in the research, as shown in Figure 1.

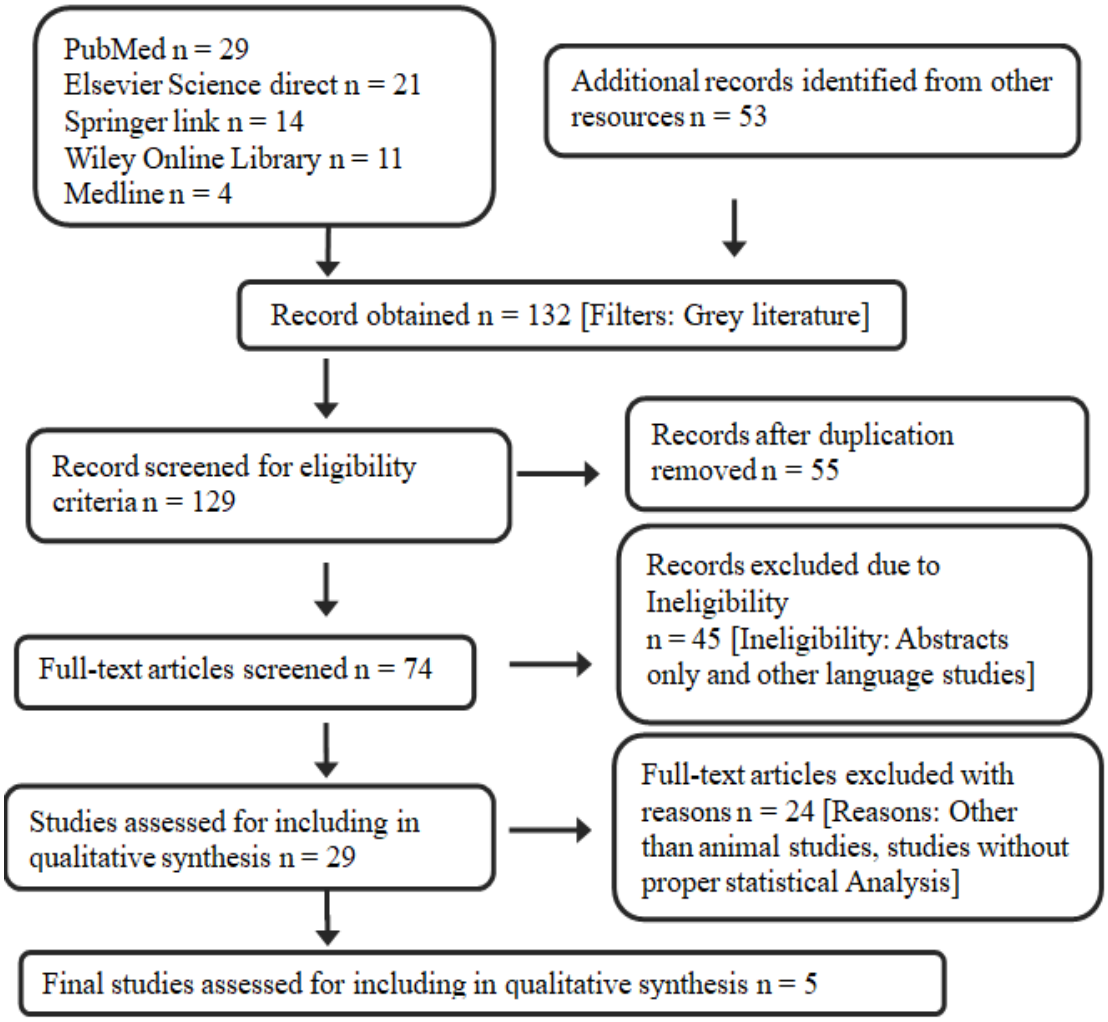

Figure 1: PRISMA flowchart illustrating how the studies are included in this Systematic Review.

Table 1: Description of all the included studies in the Systematic Review

First author	Year of Study	Place of study	Study design	Sample size	Intervention	Methods of Measurement
Mahboubeh Tajaldini [15]	2020	Iran	Animal studies	6-8 weeks old 30 male nude mice were randomly divided into 6 groups: Control, Orange Peel Extract (OPE), Narinigin (NR), Combination of Doxorubicin (Dox) and NR, Dox + OPE+ DOX	Mice received 50 mg/kg OPE, 50 mg/kg NR, 0.5 mg/kg DOX alone and combined with OPE and NR daily for 14 days.	Cell viability assay, Cell cycle assay, Gene expression assay and measurement of serum MDA, SOD, and TAC activity
Min-Hsuing Pan [16]	2012	China	Animal studies	5-6 weeks old 33 female mice in Group 1: Ac/Ac Group 2: Ac/ TPA Group 3: 100µL (Gold Lotion, GL/TPA	Mice were treated topically with 100 or 200 L of GL 30 min prior to the treatment of 10 nmol TPA, and they were killed 2 and 4 h, respectively, after the TPA treatment.	Measurement of epidermal hyperplasia, Western blot technique, RT-PCR for iNOS and COX-2 gene expression, High-Performance Liquid

						Chromatography (HPLC), Densitometric analysis
Takuji Tanaka [17]	2008	Japan	Animal studies	75 male mice aged 5 wk (Charles River Japan Inc., Tokyo, Japan) were divided into 10 experimental and control groups	Study I: Group 1: Single intraperitoneal inj. Azoxymetahene (AOM) for 17 weeks Group 2: 0.01% auraptene in diet 3: 0.05% auraptene in diet 4: 0.01% collinin in diet 5: 0.05% collinin in diet 6: Single dose of AOM 7: 1% DSS for 7 days 8: 0.05% auraptene in diet 9: 0.05% collinin in diet 10: Untreated mice Study II: 36 homozygous db/db, 40 heterozygous db/+, and 40 littermate controls (+/+) Group 1: Basal diet Group 2: 0.02% Citrus Unshiu Segment Membranes (CUSM) for 7 weeks Group 3: 0.1% CUSM for 7 weeks Group 4: 0.05% CUSM for 7 weeks	PCNA-labelling Index – Cyclooxygenase (COX)-2, inducible Nitric Oxide Synthase (iNOS), Interleukin-1beta (IL-1β), and Tumor Necrosis Factor-alpha (TNF-α)
Keiko sakata [18]	2004	Japan	Animal studies	135 male F344 rats aged 4 weeks	Experiment 1: Twenty F344 rats were divided into five groups at 5 weeks of age. At 6 weeks of age, N, N-di ethylnitrosamine (DEN) with 40 ppm in drinking water was given for 5 weeks in groups 1–3 to induce hepatocellular enzyme-altered foci (EAF). Group 1: No further treatments and maintained on a diet without Auraptene (AUR). Group 2: Diet containing 100 ppm AUR for 7 weeks. Group 3: Diet containing 500 ppm AUR for 7 weeks. Group 4: 500 ppm AUR-containing diet. Group 5: Control. Experiment 2 was conducted to support the results of the EAF bioassay 135 rats were allocated to seven experimental and control groups. Groups 1–5 received	Immunohistochemical staining for glutathione S-transferase (GST-P), transforming growth factor (TGF-α), Proliferating Cell Nuclear Antigen (PCNA), and single-stranded DNA (ssDNA) was performed by a standard method using the LSAB universal kit (Dako, Glostrup, Denmark). Quantitative Assessment of Hepatocellular EAF and Neoplasms

					drinking water containing 40 ppm DEN for 5 weeks to induce hepatocellular neoplasms. Groups 2-3: Diets containing 100 and 500 ppm AUR for 7 weeks. Groups 4-5: 100 and 500 ppm AUR-containing diets for 25 weeks. Group 6: Diet containing 500 ppm AUR (32 weeks). Group 7 as untreated controls.	
Akira Murakami [19]	2000	Japan	Animal studies	Each group consists of 15-17 6-week-old female mice. **Group 1:** Acetone (Ac) Ac/Ac⟶Ac/Ac **Group 2:** Acetone-TPA⟶ acetone-TPA **Group 3:** Nobiletin-TPA⟶ nobiletin-TPA **Group 4:** Nobiletin TPA⟶ acetone-TPA **Group 5:** Acetone-TPA⟶ nobiletin-TPA	Group 1: 12-O-tetradecanoylphorbol-13-acetate (TPA) (1.6 nmol in 100 ml of acetone) twice a week for 20 weeks. Group 2-5: Nobiletin (40, 80, 160, or 320 nmol in 100 ml of acetone) 40 min before each TPA treatment**.**	NO Generation Test, Western blotting technique, Measurement of H_2O_2, Edema Formation in Mouse, Histological Examination, PCNA Immunohistochemistry, and PGE_2 Determination.

Table 1 represents the characteristics of the intervention that were included in the analysis. All of the aforementioned research, written by Akira Murakami et al., Mahboubeh Tajaldin et al., Min-Hsuing Pan et al., Keiko Sakata et al., and Takuji Tanaka et al., involved the consumption and administration of citrus peels on mice and rodents for the prevention of cancer.

Table 2: Characteristics of the results and inference of each study

First author	Result	Inference
Mahboubeh Tajaldin et al. 2020	In the fifth week, NR and OPE reduced the sizes of the tumours close to 30% that in control groups received an effective anticancer treatment by itself ($p<0.01$). DOX injection proved most effective for elimination of tumours. DOX combination with NR or OPE has no significant change in its antitumor activity.	OPE can reduce the esophageal cancer stem cells derived tumor size, protecting from the side effects of DOX chemotherapy drugs by reducing oxidative stress and maintaining body weight
Min-Hsuing Pan et al. 2012	The animals in the Ac/TPA group exhibited 16 ± 3 papillomas per mouse and 100% incidence of skin tumors at 20 weeks, while mice treated with acetone exhibited no tumor development. When GL was applied, the number of papillomas was 12 ± 4, which is a 25% reduction compared to the Ac/TPA group ($p < 0.05$). Tumor incidence was 100% in the Ac/TPA group, whereas the GL-treated group showed a significant reduction of 18%	Pre-treatment with 100μL and 200μL GL prior to TPA application significantly inhibited the expression of the inflammatory enzyme iNOS gene and protein but not COX-2.
Takuji Tanaka et al. 2008	The incidence (50–60% decrease) and multiplicity (67–80% reduction) of colonic adenocarcinomas caused by AOM and dextran sodium sulfate (1% in drinking water) were dramatically reduced by dietary feeding with auraptene and collinin at dosage levels of 0.01% and 0.05%. Administration with CUSM at 3 doses in the diet significantly inhibited the development of aberrant crypts foci induced by 5 weekly subcutaneous injections in db/db male mice with 53%	Citrus compounds including auraptene, collinin and CUSM inhibit inflammation and obesity related colon carcinogenesis.

	inhibition by 0.02% CUSM, 54% inhibition by 0.1% CUSM, and 59% inhibition by 0.5% CUSM ($p < 0.05$).	
Keiko Sakata et al. 2004	Experiment 1: The results of quantitative analysis of hepatocellular EAF positive for GST-P and TGF-α and the reduction in the number of TGF-α positive EAF by feeding 500 ppm AUR was statistically significant ($p<0.005$). Experiment 2: The frequencies of hepatocellular carcinoma Group 1 – 83% Group 2 - 67% Group 3 - 33%; $p < 0.000511$ Group 4 - 15%; $p < 0.000006$ Group 5 - 11%; $p < 0.000002$	Citrus antioxidant AUR acts as a chemopreventive agent against DEN-induced hepatocarcinogenesis.
Akira Murakami et al. 2000	Two different phases of skin irritation brought on by double TPA treatment were markedly reduced by nobiletin. Additionally, it inhibited prostaglandin E2 release, cyclooxygenase-2, and inducible NO synthase protein production. At dosages of 160 and 320 nmol, nobiletin prevented the development of skin cancers caused by dim-ethylbenz[a]anthracene (0.19 mmol)/TPA (1.6 nmol) by lowering the number of tumors per mouse by 61.2% ($p < 0.001$) and 75.7% ($p < 0.001$), respectively.	Citrus flavonoid nobiletin was found to be a functionally novel antitumor promoter by working in both the priming and activation stages in mouse skin.

Table 2 provides a comprehensive summary of the findings from various studies that investigated the effects of administering and dietary additions of citrus peel to mice as a potential preventive measure against cancer. The table outlines the key results from each study.

Table 3: Assessment of Risk of Bias of all the included studies

Author name	Randomization	Allocation Concealment	Comparison group	Confounding	Experimental conditions	Blinding	Complete outcome data	Exposure Characterization	Outcome Assessment	Outcome Reporting	No other threats
Mahboubeh Tajaldin et al. 2020											
Min-Hsuing Pan et al. 2012											
Takuji Tanaka et al. 2008											
Keiko Sakata et al. 2004											
Akira Murakami et al. 2000											

Definitely low risk of bias
Probably low risk of bias
Probably high risk of bias
Definitely high risk of bias
NA – Not Applicable

Table 3 shows the risk of bias assessment of all the included studies according to the OHAT [Office of Health Assessment and Translation] tools [14]

DISCUSSION

Flavonoids have garnered interest and have been evaluated in several clinical trials for their positive potential benefits in several human diseases, including life-threatening diseases such as cancers because they exert strong antioxidant properties.Reframing dietary patterns by mitigating flavanoid requirements is proven to be the best and most cost-effective strategy for cancer prevention. This study focused on the bioactive substances found in citrus peel extract from all diets high in flavonoids.

The citrus peels comprise a wide array of bioactive compounds, Naringenin and Hesperetin show strong antiproliferative activity against human breast cancer cells, prostate, melanoma, lung, and colon cancer cells [20]. By upregulating inhibitors specific for the cytochrome P450 family members CYP1B1 and CYP1A1, nobiletin significantly increases the cytostatic effect in (ER+) MCF-7 breast cancer cells [21]. C. reticulata peels extracts and essential oils exhibited striking activity against the DLA cell line in MTT3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. The aqueous extract of C. reticulata peel facilitated the cell cycle arrest of DLA in the G0/G1 phase. This was followed by nuclear condensation, membrane blebbing, the production of apoptotic bodies, DNA damage, and death [22].

Akira Murakami et al. (2000) study demonstrated the topical application of nobiletin in inhibiting the proliferation of skin tumors in a dose-dependent manner based on the suppressive effects of biochemical markers associated with oxidative stress, edema formation, epidermal thickness, leukocyte infiltration, hydrogen peroxide production, and the rate of proliferating cell nuclear antigen-stained cells and inflammation. Topical application of nobiletin at doses of 160 and 320 nmol inhibited the multiplicity of skin tumors in a dose-dependent manner. Even though experimental conditions were different, nobiletin inhibited tumor formation in the mouse skin model even at 1–25 mmol concentrations, whereas resveratrol did not [19]. This study adopted the activity-guiding separation approach, which might soon be a viable method to discover potent chemopreventive drugs. A study by Hakim IA et al. (2000) showed a dose-response relationship between human malignancies and limonene in citrus fruits. The case-control study reported different risk patterns regarding the consumption of citrus fruits or juices and the specific consumption of citrus peel. Citrus consumption has been perceived to have different effects based on the type of product consumed [23]. There is a very significant correlation between the consumption of citrus peel and human cancers, but not between the consumption of citrus fruits or juices. The main limitation of the study was its small sample size, which prevented it from being widely generalized. AUR treatment may inhibit cell proliferation, prevent the emergence of new vasculature required for carcinogenesis, inhibit oxidative damage, and induce phase II drug detoxifying enzymes, without influencing phase I enzyme activity in the liver. These factors may be the cause of AUR's inhibitory effect on DEN-induced hepatocarcinogenesis.

Mahboubeh Tajaldin et al. (2020) study illustrated the protective effects of OPE against the side effects of Dox regarding body weight loss. OPE was reported to possess radical scavenging properties. The study also demonstrated that OPE and NR significantly restored the antioxidant defense system by decreasing Malondialdehyde (MDA) levels [15]. To determine whether this non-toxic supplement can be used for a prolonged period, clinical trials must be conducted to determine the pharmacokinetics and pharmacodynamics properties.

Min-Hsiung Pan et al. (2012) formulated a citrus peel product made of *navel oranges, citrus hassaku, citrus limon, citrus natsudaidai, citrus miyauchi,* and *Satsuma* called “Gold Lotion” cosmetically to protect skin from UV radiation. The study demonstrated that the topical application of Gold Lotion inhibited carcinogenesis through activation of iNOS gene expression and mRNA and inhibition of COX-2, Ornithine Decarboxylase (ODC), and Vascular Endothelial Growth Factor (VEGF) expression [16]. Tanaka Takuji et al. study (2008) identified the efficacy of chemoprotective dietary citrus compounds such as Auraptene, Collinin, and Citrus Unshiu Segment Membrane (CUSM) in animal models. According to the results of the study, all three compounds inhibit tumorogenesis, but the dose-response relationship of CUSM in inhibiting the development of aberrant crypt foci was clearly established [17]. This makes the study stand out from other studies.

Keiko Sakata et al. (2004) in his study stated two opposing outcomes of AUR: It inhibits oxidative damage as well as reduces cellular apoptosis, which opens the door for the development of neoplasia [18]. The study, therefore, underlined that the maximum beneficial effects can be obtained only by demonstrating a dose-response relationship. To produce the highest bioactive compound, Nooshin Koolji et al. (2020) identified a number of extraction techniques, such as hot water extraction, solvent extraction, alkaline extraction, ultrasound-assisted extraction, supercritical fluid extraction, microwave-assisted extraction, and enzyme-assisted extraction [24].

This study has several limitations, including the lack of studies. Secondly, more must be done to examine the long-term effects of human interventional trials. Thirdly, precise dose-response relationships for bioactive compounds are essential to avoid potential adverse effects.

CONCLUSION

Based on the findings of various studies, the systematic review assesses the efficacy of citrus peel

in reducing cancer risk. Using these results, it was concluded that citrus peel is capable of reducing the risk of cancer through its anti-inflammatory and antioxidant properties. To confirm these benefits, a large-scale clinical trial on a large number of subjects is necessary. There may be a reduction in cancer risk and a better quality of life associated with the consumption of citrus peels.

CONFLICT OF INTEREST: Authors declare no conflict of interest.

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REFERENCES

1. World Health Organization. Cancer. 2022 Available at https://www.who.int/news-room/fact-sheets/detail/cancer [accessed on 4 Oct 2024]
2. Prabu D, Gousalya V, Rajmohan M, Dinesh M D, Bharathwaj VV, Sindhu R, Sathiyapriya S. Need Analysis of Indian Critical Health Care Delivery in Government Sectors and Its Impact on the General Public: A Time to Revamp Public Health Care Infrastructure. Indian J Crit Care Med 2023; 27(4): 237-45.
3. World Health Organization. Global Cancer burden growing, amidst mounting need for services. 2024. Available at https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services [accessed on 4 Oct 2024]
4. Sloan FA, Gelband H and editors. Cancer Control Opportunities in Low- and Middle-Income Countries. Institute of Medicine (US) Committee on Cancer Control in Low- and Middle-Income Countries; Washington (DC): National Academies Press (US), 2007.
5. Chen YC, Malfertheiner P, Yu HT, Kuo CL, Chang YY, Meng FT, Wu YX, Hsiao JL, Chen MJ, Lin KP, Wu CY, Lin JT, O'Morain C, Megraud F, Lee WC, El-Omar EM, Wu MS, Liou JM. Global Prevalence of *Helicobacter pylori* Infection and Incidence of Gastric Cancer Between 1980 and 2022. Gastroenterology 2024;166(4): 605 – 19.
6. David Rakel MD, Andrew Weil MD. Philosophy of Integrative Medicine. Integrative Medicine (Fourth Edition), 2018, pp: 2-11.e1
7. Bocci V. The Potential Toxicity of Ozone: Side Effects and Contraindications of Ozonetherapy. Ozone 2010;24: 75–84.
8. Ngomdir L, Bharathwaj VV, Nimmy P, Sindhu R, Dhamodhar D, Sathiyapriya S, Prabu D, Rajmohan M. Therapeutic Use of Anti-Sclerostin Antibody in the Treatment of Multiple Myeloma: A Systematic Review. J Pharm Bioallied Sci 2023;15(Suppl 1): S738-S741.
9. Afshin A, Sur PJ, Fay KA, Cornaby L, Ferrara G, Salama JS, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 2019;393(10184): 1958-1972.
10. Xiu-Min Chen, Andrew R Tait, David D Kitts. Flavonoid composition of orange peel and its association with antioxidant and anti-inflammatory activities. Food Chemistry 2017;218: 15-21.
11. Kopustinskiene DM, Jakstas V, Savickas A, Bernatoniene J. Flavonoids as Anticancer Agents. Nutrients 2020;12(2): 457.
12. Muhammad Fayyaz ur Rehman, Aima Iram Batool, Rahman Qadir, Mehwish Aslam. Chapter 18 - Hesperidin and naringenin. A Centum of Valuable Plant Bioactives, ISBN 9780128229231, Academic Press 2021: 403-444.
13. Mehmood T, Afzal A, Anwar F, Iqbal M, Afzal M, Qadir R. Variations in the Composition, Antibacterial and Haemolytic Activities of Peel Essential Oils from Unripe and Ripened Citrus limon (L.) Osbeck Fruit. Journal of Essential Oil Bearing Plants 2019; 22: 1-10.
14. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Office of Health Assessment and Translation (OHAT). Division of the National Toxicology Program. National Institute of Environmental Health Sciences. 2019. https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/pubs/handbookmarch2019_508.pdf [accessed on 7 Aug 2024]
15. Mahboubeh T, Firooz S, Ayyoob K, Azim G, Jahanbakhsh A. Protective and anticancer effects of orange peel extract and naringin in doxorubicin treated esophageal cancer stem cell xenograft tumor mouse model, Biomedicine & Pharmacotherapy 2020;121: 109594.
16. Min-Hsiung P, Shiming Li, Ching-Shu L, Yutaka M, Michiko S, Chi-Tang Ho. Inhibition of citrus flavonoids on 12-O-tetradecanoylphorbol 13-acetate-induced skin inflammation and tumorigenesis in mice. Food Science and Human Wellness 2012;1(1): 65-73.
17. Tanaka T, Yasui Y, Ishigamori-Suzuki R, Oyama T. Citrus compounds inhibit inflammation- and obesity-related colon carcinogenesis in mice. Nutr Cancer 2008;60 (Suppl 1): 70-80.
18. Sakata K, Hara A, Hirose Y, Yamada Y, Kuno T, Katayama M, Yoshida K, Zheng Q, Murakami A, Ohigashi H, Ikemoto K, Koshimizu K, Tanaka T, Mori H. Dietary supplementation of the citrus antioxidant auraptene inhibits N,N-diethylnitrosamine-induced rat hepatocarcinogenesis. Oncology 2004;66(3): 244-52.
19. Murakami A, Nakamura Y, Torikai K, Tanaka T, Koshiba T, Koshimizu K, Kuwahara S, Takahashi Y, Ogawa K, Yano M, Tokuda H. Nishino H, Mimaki Y, Sashida Y, Kitanaka S, Ohigashi H. Inhibitory Effect of Citrus Nobiletin on Phorbol Ester-induced Skin Inflammation, Oxidative Stress, and Tumor Promotion in Mice. Cancer Research 2000;60: 5059–5066.
20. Manthey J, Guthrie N. Antiproliferative activities of citrus flavonoids against six human cancer cell lines. J Agric Food Chem 2002;50(21): 5837–43.
21. Surichan S, Androutsopoulos VP, Sifakis S, Koutala E, Tsatsakis A, Arroo RR, Boarder MR. Bioactivation of the citrus flavonoid nobiletin by CYP1 enzymes in MCF7 breast adenocarcinoma cells. Food Chem Toxicol 2012;50(9): 3320–8.
22. Garg M, Lata K, Satija S. Cytotoxic potential of few Indian fruit peels through 3-(4,5-dimethylthiazol-yl)-2,5-diphenyltetrazolium bromide assay on HepG2 cells. Indian J Pharmacol 2016;48(1): 64-8.

23. Hakim IA, Harris RB, Ritenbaugh C. Citrus peel use is associated with reduced risk of squamous cell carcinoma of the skin. Nutrition and cancer 2000;37(2): 161-168.

24. Koolaji N, Shammugasamy B, Schindeler A, Dong Q, Dehghani F, Valtchev P. Citrus Peel Flavonoids as Potential Cancer Prevention Agents. Curr Dev Nutr 2020;4(5): nzaa025.