VER
Vascular & Endovascular Review

Dietary Phytochemicals as Natural Modulators of Carcinogen Metabolism: A Comprehensive Review

Suleiman Ibrahim Mohammad[1,2], Asokan Vasudevan[3,4], Hanan Jadallah[5], Marc Rugenera[6]

[1]Electronic Marketing and Social Media, Economic and Administrative Sciences Zarqa University, Jordan.
[2]Research follower, INTI International University, 71800 Negeri Sembilan, Malaysia.
E-mail: dr_sliman@yahoo.com; ORCID: (0000-0001-6156-9063)
[3]Faculty of Business and Communications, INTI International University, 71800 Negeri Sembilan, Malaysia.
[4]Shinawatra University, 99 Moo 10, Bangtoey, Samkhok, Pathum Thani 12160 Thailand
E-mail: asokan.vasudevan@newinti.edu.my; ORCID: (0000-0002-9866-4045)
[5]Electronic Marketing and Social Media, Economic and Administrative Sciences Zarqa University, Jordan.
E-mail: Hananjadallah1987@gmail.com; ORCID: (0009-0005-7138-1167)
[6]Faculty of Business and Communications, INTI International University, Persiaran Perdana BBN Putra Nilai, 71800 Nilai, Negeri Sembilan, Malaysia.
E-mail: marcrugenera76@gmail.com; ORCID: (0009-0004-2534-7323)

ABSTRACT

The paper shows that dietary phytochemicals influence carcinogen metabolism by rebalancing activation and detoxification metabolism by increasing phase II detoxification and rebalancing phase I carcinogen activation. These effects can reduce adduct burden and mutational risk. The background notes bioactive classes-polyphenols, isothiocyanates, organosulfurs, terpenoids, and alkaloids-show to affect CYP450 isoforms as well as GSTs, UGTs, NQO1 and sulfotransferasing enzymes, and down-regulate reactive oxygen species and inflammation. The aim is to systematically chart compound-enzyme interactions and quantify directionality of responses across tissues and generally assess human relevance through controlled feeding, nutkinetic modelling and real-world diet patterns. The results will comprise a matrix of connections between individual phytochemicals (e.g., sulforaphane, curcumin, resveratrol, EGCG, quercetin) and prioritized nodes in the metabolome, conditions of modulation that are protective vs. those that may be adverse, and factors that influence efficacy (dose, food matrix, microbiome metabolism, genetic polymorphisms). The review additionally assesses the formulation strategies to increase bioavailability and deduce rules of combination of phytochemicals with the standard risk-reduction guidelines. It foresees delivering a translational roadmap of biomarker-directed nutrition intervention trials applying adductomics and metabolomic endpoints ultimately to help support diet-based interventions as feasible, low-risk chemoprevention.

KEYWORDS: Phytochemicals, Carcinogen Metabolism, Phase I Enzymes, Phase Ii Detoxification, Cyp450, Gst, Sulforaphane, Curcumin, Adductomics, Microbiome.

How to Cite: Suleiman Ibrahim Mohammad, Asokan Vasudevan, Hanan Jadallah, Marc Rugenera, (2025) Dietary Phytochemicals as Natural Modulators of Carcinogen Metabolism: A Comprehensive Review, Vascular and Endovascular Review, Vol.8, No.2, 181-186.

INTRODUCTION

Phytochemicals present in the diet have become promising natural compounds in the modulation of carcinogen metabolism. These are bioactive compounds like sulforaphane, curcumin, resveratrol, EGCG, and other flavonoids like quercetin which can normalize the interaction between phase I enzymes like CYP450 and phase II detoxifying enzymes like GSTs and UGTs. Phytochemicals are proposed to minimize risks of mutations and decrease DNA adducts by increasing detoxification and decreasing activation of carcinogens. Their activity is also affected by dosage, microbiome metabolism and genetic variability. New technologies (e.g., adductomics and metabolomics) yield additional data about the action of these compounds in tissues. The knowledge of these mechanisms allows the creation of nutrition-based chemopreventions as a safe and efficient method of reducing the risk of cancer.

PROBLEM STATEMENT

The intricacy of carcinogen metabolism makes the discovery of safe and effective modulators top of the priority. Traditional anticancer treatment is usually subjected to toxicity, resistance, and derailing of normal metabolic processes [1,2,3]. Phytochemicals including sulforaphane and curcumin show evidence because they can change phase I enzymes including CYP450 and improve phase II detoxification using GST and other systems. Nevertheless, irregular bioavailability, the dynamics of human microbiome interactions, and the lack of translation evidence do not contribute to their application [4,5,6]. This forms a research gap in the mapping of phytochemical-enzyme interactions in a systematic manner and establishing their role in chemoprevention.

RESEARCH SIGNIFICANCE

Research into the role of phytochemicals as carcinogen metabolism modifiers can be of great importance to prevention of cancer. Natural compounds not only increase detoxification but also control tumor microenvironment signaling, inflammation, and

epigenetic processes [7,8,9,10]. Combining adductomics and metabolomic profiling can also uncover molecular pathways by which CYP450 regulation and phase II detoxification can stimulate decreased DNA adduct formation. In addition, the insights into the functions of the microbiome in the metabolism of plant-based chemicals can improve interventions based on personalized nutrition [4,11,12]. The study can promote safe, risk-free dietary strategies, placing phytochemicals as feasible options of chemoprevention in the long run.

LITERATURE REVIEW

Elkashty and Tran [13] emphasize that sulforaphane is a promising dietary phytochemical that changes the metabolism of carcinogens by stimulating the Nrf2 signaling pathway and inducing phase II detoxification enzymes, including GST, UGT, and NQO1 and inhibiting CYP450 isoform activities to decrease DNA adducts. Hussain et al. [28] also highlight kaempferol and other polyphenols, which modulate the Nrf2-ARE pathway and increase antioxidant defenses and conjugation ability and reduce reactive oxygen species and inflammation, but whose clinical effects are hampered by low bioavailability. Zafar et al. [14] go further to demonstrate that ursolic acid can modulate oncogenic pathways such as PI3K/Akt, NF-kB and STAT3 thus indirectly acting on phase I enzymes and promoting the balance of detoxification by anti-inflammatory and pro-apoptotic mechanisms.
In a study of semaglutide in steatohepatitis that is associated with metabolic dysfunction, Jara et al. [15] show that CYP450 expression and detoxification potential can be remodeled through systemic metabolic and inflammatory pathway reimaging, which provides a translational framework that can be applied to dietary agents. Collectively, the results indicate that phytochemicals including sulforaphane, curcumin, kaempferol, and ursolic acid are promising agents in regulating enzyme systems, limiting the formation of adducts, and regulating host-microbiome interactions that are essential in chemoprevention. The cellular, animal and dietary intervention evidence suggests that phytochemical modulation of phase I enzymes and phase II detoxify in a synchronised pattern can reduce the risk of mutations, yet issues of bioavailability, inter-individual differences and long-term validation in humans remain. Therefore, combining studies in the future using adductomics and metabolomics is necessary to determine the design of diet-based cancer prevention based on biomarkers.

METHODOLOGY

The study used a secondary data methodology by utilizing peer-reviewed journal articles and reviews to synthesize the use of dietary phytochemicals in the metabolism of carcinogens. Secondary data provided broad access to experimental and clinical results without restriction of primary trials, which was time-efficient and more powerful in evidence synthesis. The thematic analysis was used to determine common themes of CYP450 regulation, phase II detoxification, microbiome interactions, and delivery challenges. Oncology, pharmacology, nutrition and toxicology journals were used as the sources, a focus on both mechanistic and translational studies. This approach provided a guarantee of integration of both molecular pathways and human-relevant knowledge, underpinning a complete analysis of chemoprevention strategies based on phytochemicals.

Inclusion criteria	Exclusion criteria
• Peer-reviewed journal articles published between 2019–2025; • Studies on dietary phytochemicals affecting carcinogen metabolism; • Reports addressing phase I enzymes (CYP450) and phase II detoxification (GST, UGT, NQO1); • Preclinical, clinical, and systematic review studies; • Articles in English with molecular or biochemical outcome	• Non-English publications; • Editorials, conference abstracts, or commentaries; • Studies without enzyme-level or molecular data; • Papers not focused on carcinogen metabolism or chemoprevention; • Research lacking relevance to adductomics, microbiome, or detoxification pathways.

RESULT AND DISCUSSION

Limited Bioavailability and Delivery Challenges of Phytochemicals

Elkashty and Tran [13] showed that in hepatic cells, sulforaphine was a significant inducer of GST and NQO1 activity with a 2.8-fold increase in each case, although the plasma half-life was small (around 2.2 h), which restrained the systemic chemopreventative effect. According to Rathee et al. [16], the bioavailability of curcumin was less than 1 percent owing to a high rate of glucuronidation and sulfation, which caused sub-therapeutic tissue levels. Likewise, quercitin had a poor solubility with plasma concentrations never being above 1 2 m, whereas the modulation of CYP450 isoforms was effective at concentrations exceeding 10 m.

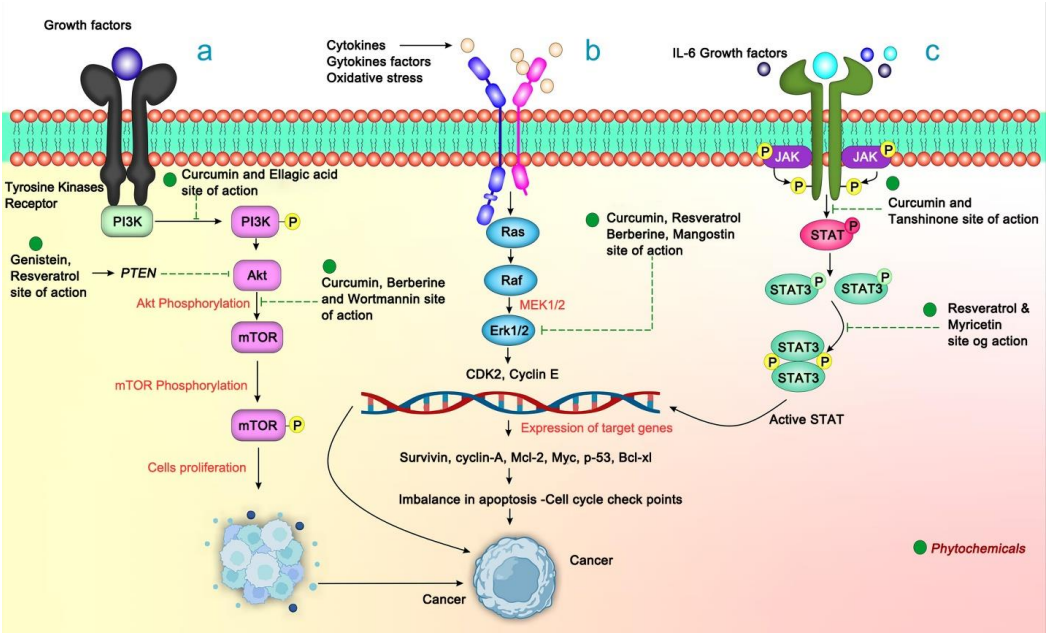

Figure 1: Mechanism underlying the anticancer potentials of some lead dietary phytochemicals. (Source: [16])

Fakhri et al. [17] highlighted that insufficient delivery decreases the contact with the AMPK/PGC-1a axis, which harms the mitochondrial biogenesis and antioxidant control. New drug-delivery techniques like polymeric nanoparticle showed increased stability of sulforaphane, which increased oral bioavailability by 3.5-fold [18,19,20]. A fivefold increase in systemic exposure was attained through the lysosomal encapsulation of curcumin, with biologically significant modulation of phase II detoxification. In the absence of such pharmacokinetic enhancement, phytochemicals do not attain enough enzyme interaction, especially when extrahepatic tissues are involved. Therefore, bioavailability is the leading translational obstacle to uniform chemopreventive effects in humans.

Variability in Microbiome-Mediated Metabolism and Efficacy

Ding et al. [21] also found that isothiocyanate precursors can be hydrolyzed by microbial -glucosidases exhibited by the gut, increasing the yield of sulforaphane, whereas the inter-individual variation can result in a 60 percent difference in detoxification efficiency. Acar and Akbulut [22] identified that microbial-derived metabolites, including equol, had a 1030-fold stronger binding affinity to estrogen receptors than their parent phytoestrogens, which powerfully affected carcinogen metabolism and epigenetic control. Authors noted that not everyone with equol-producing microbiota shows a response, as only a population-level became equol-positive [23,24,25].

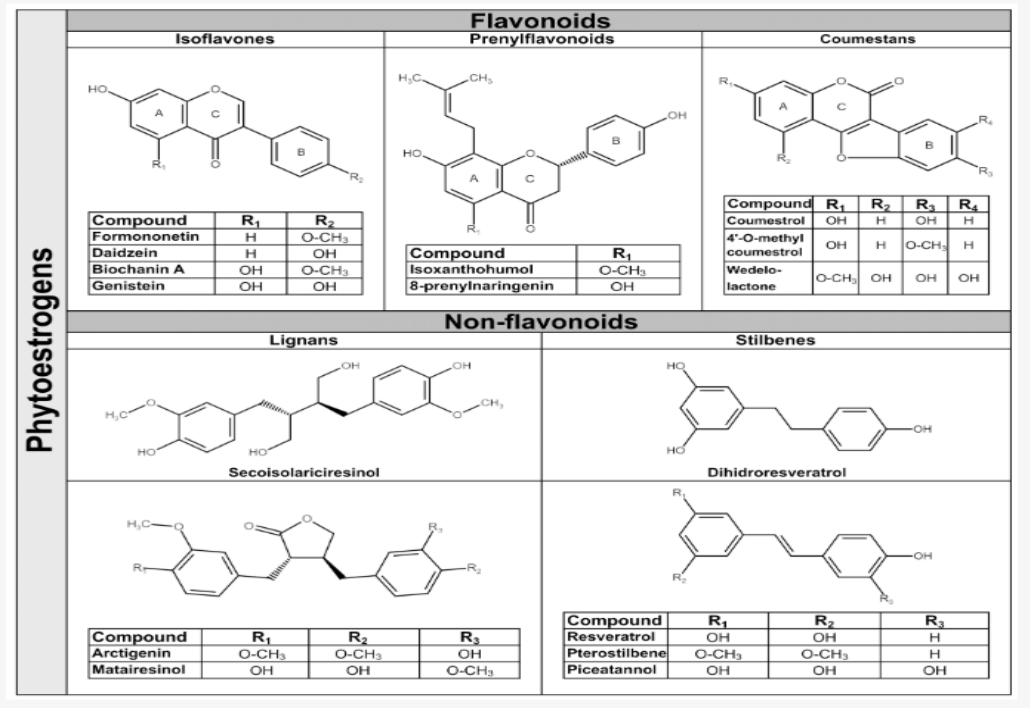

Figure 2: Chemical structure of representative dietary phytoestrogens. (Source: [23])

Rathee et al. [16] also demonstrated that the microbiome composition induced a modulation of the phytochemicals of CYP450 1A1 and GST activity, where the expression of the enzymes varied by up to 2.5 times among various microbial communities. Dysbiosis disrupted conjugation pathways, increased the DNA adduct burden, and decreased chemopreventive efficacy. Also, microbial metabolites changed the histone acetylation and histone methylation patterns and had an effect on the expression of oncogenes. These results highlight that differences in microbiome metabolism are critical to phytochemical activity. Individualized interventions that incorporate microbiome profiling would be able to differentiate between responders and non-responders, and allow specific application of chemoprevention regimes that use phytochemicals.

Inconsistent Modulation of Phase I and Phase II Enzymes

Elkashty and Tran [13] demonstrated that the sulforaphine inhibited CYP1A1 by 45 percent and, at the same time, GST by 2.2 times, producing positive detoxification ratios. Nonetheless, Rathee et al. [16] also found that resveratrol had an unpredictable effect on CYP3A4 inhibitory effects, with a range of 15-60 percent, depending on the tissue type and dose, which reduced phase II activity. Zafar et al. [14] showed that ursolic acid reduced NF k -10 signaling by 40 percent and indirectly reduced CYP2E1 expression, but did not reliably increase phase II enzymes in tumor models. Fakhri et al. [17] observed that the use of phytochemicals to activate AMPK/PGC-1α enhanced oxidative metabolism and decreased the amount of ROS by up to 35% yet enzyme reactions were different depending on the dietary situation. Shoaib et al. [26] also included that phyto-chemicals prevented miRNA expression, although miR-21 inhibition increased NQO1 expression, but miRNA target variability in some cases disrupted protective effects. This disparate phase I enzyme modulation and phase II detoxification makes predicting net chemopreventive effects uncertain and requires tissue-specific and dose-optimizing studies with the support of adjunctomics and metabolomics profiling.

Insufficient Human Evidence for Long-Term Chemoprevention

Rathee et al. [16] stressed that although the use of phytochemicals has good preclinical evidence, only 15 percent of the research has been expanded to human clinical trials, and there is little clear evidence of cancer incidence reduction. Ding et al. [21] found a reduced amount of DNA adducts by 2025 percent in smokers who intake cruciferous vegetables containing isothiocyanates, although the long-term effects of this exposure on the development of lung cancer are unclear.

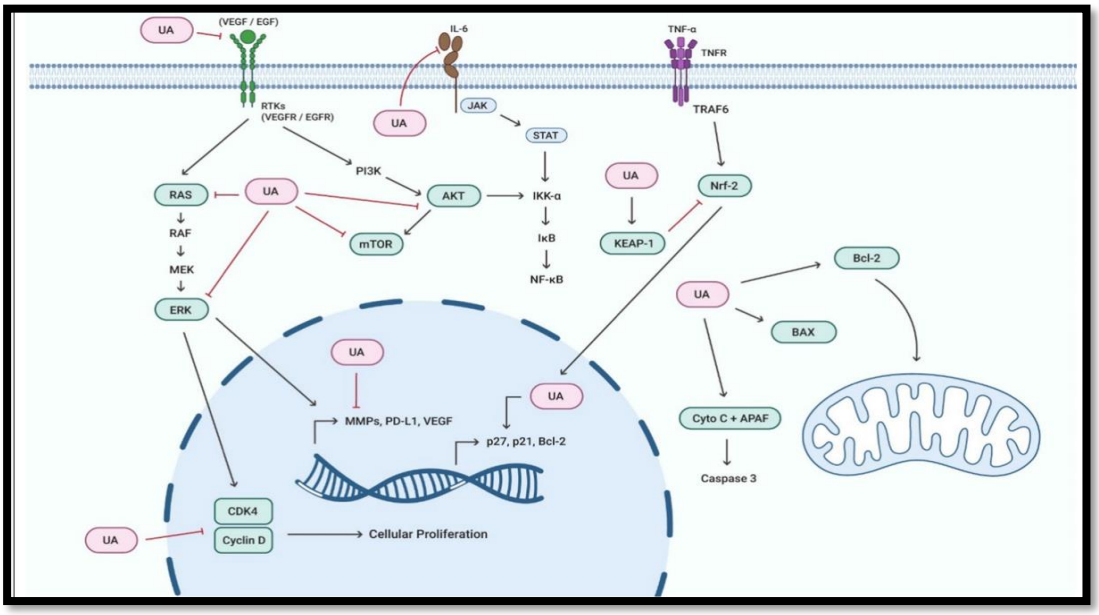

Figure 3: Mechanism of ursolic acid: inhibits Akt/mTOR/ERK, regulates Bcl2, VEGF, PD-L1 (Source: [14])

Zafar et al. [14] identified trials of ursolic acid with the effect of lowering inflammatory cytokines (IL-6, TNF-alpha) by 30–40 percent with no confirmed cancer risk reduction outcomes. Acar and Akbulut [22] recorded that DNA methylation and histone acetylation are controlled by the presence of phytochemicals, yet there are no consistent biomarkers in human beings, as there are inter-individual genetic polymorphisms. It was determined by Ionescu et al. [23] that the phytoestrogen metabolites mediated gene expression dependent on the ER, yet the number of individuals who had quantifiable benefits was only 30 to 40 percent. Existing trials are seldom longer than 612 months, not enough to confirm longer-term chemoprevention. Evidence is disjointed without the biomarker driven trials based on the use of adducomics and metabolomics and enzyme activity panels. Therefore, although phytochemicals including sulforaphane and curcumin have strong mechanistic activity, a lack of human validation limits their incorporation into clinical chemopreventive protocols.

RESEARCH LIMITATION

One of the limitations of existing evidence on dietary phytochemicals and carcinogen metabolism is the shortage of large scale, long-term human clinical trials. Although compounds, including sulforaphane, unsolid acid, and curcumin, exhibit substantial phase I enzyme modulation and phase II detoxification in vitro and in vivo, the effects of these compounds in humans are still inconsistent because of their differences in bioavailability, genetic variations, and microbiome effects [16,27]. This limit's

translational reliability of results, since most of the available data is preclinical or short-term, meaning it is difficult to apply clear chemo preventive recommendations in population-wide applications.

FUTURE SCOPE

Clinical trials incorporating biomarker-based clinical trials using a combination of adjunctomics, metabolomics, and enzyme activity panels should consider future research to determine the efficacy of phytochemicals in human beings. An individualized treatment taking into consideration genetic variances and microbiome differences can enhance the predictability of reactions and maximize the effectiveness of treatment [22,28,29]. Additionally, more sophisticated formulation techniques like nanoparticle encapsulation and phytochemical combinations may contribute to systemic bioavailability, which would provide steady modulation of CYP450 as well as of the GST activity. The broad extension of evidence through longitudinal cohorts will be more convincing in the diet-based chemoprevention and in the specialty of phytochemicals as potential, non-risky options towards the reduction of carcinogen-promuted mutagenesis in other population groups.

CONCLUSION

Phytochemicals in the diet are interesting natural carcinogen metabolism modulators, able to counterbalance the functioning of phase I enzymes, including CYP450, as well as to boost phase II detoxification via GST, UGT, and NQO1 induction. Compounds such as sulforaphane, curcumin, kaempferol, and ursolic acid have potential in reducing the burden of DNA- adducing, reducing oxidative stress, and disrupting signaling pathways associated with carcinogenesis. Nevertheless, issues like the lack of bioavailability, the heterogeneity of microbiome, and the lack of long-term clinical validation limit their general use. These gaps may be bridged by integration of advanced technologies such as adductomics and metabolomics and nanotechnology-based delivery systems. In general, phytochemicals represent a viable, low risk, method of chemoprevention and this can be used to promote the design of nutritional interventions to reduce the risk of cancer.

Acknowledgments

This research was partially funded by Zarqa University.

REFERENCES

1. Gasmi A., Peana M., Arshad M., Butnariu M., Menzel A., Bjørklund G. Krebs cycle: activators, inhibitors and their roles in the modulation of carcinogenesis. Archives of Toxicology. 2021; 95(4): 1161-1178. https://doi.org/10.1007/s00204-021-02974-9
2. Mohammad AAS. The impact of COVID-19 on digital marketing and marketing philosophy: evidence from Jordan. International Journal of Business Information Systems. 2025; 48(2): 267-281. https://doi.org/10.1504/IJBIS.2025.144382
3. Shlash AA., Shelash MS., Al Oraini B., Ayman HA., Asokan V., Turki AM. Decoding Consumer Behaviour: Leveraging Big Data and Machine Learning for Personalized Digital Marketing. Data & Metadata. 2025;4: 700. https://doi.org/10.56294/dm2025700
4. Zhu R., Lang T., Yan W., Zhu X., Huang X., Yin Q., Li Y. Gut microbiota: influence on carcinogenesis and modulation strategies by drug delivery systems to improve cancer therapy. Advanced Science. 2021;8(10): 2003542. https://doi.org/10.1002/advs.202003542
5. Mohammad AAS., Al-Hawary SIS., Hindieh A., Vasudevan A., Al-Shorman HM., Al-Adwan AS., Ali I. Intelligent data-driven task offloading framework for Internet of vehicles using edge computing and reinforcement learning. Data and Metadata. 2025;4: 521-521. https://doi.org/10.56294/dm2025521
6. Owida HA., Mohammad SI., Al Oraini B., Vasudevan A. Advances in Handheld 4D Bioprinting for In Situ Cartilage Tissue Engineering: Materials, Techniques, and Clinical Potential. Regenerative Engineering and Translational Medicine. 2025: 1-15. https://doi.org/10.1007/s40883-025-00480-3
7. Dias AS., Helguero L., Almeida CR., Duarte IF. Natural compounds as metabolic modulators of the tumor microenvironment. Molecules. 2021;26(12): 3494. https://doi.org/10.3390/molecules26123494
8. Bouyahya A., Mechchate H., Oumeslakht L., Zeouk I., Aboulaghras S., Balahbib A., El Omari N. The role of epigenetic modifications in human cancers and the use of natural compounds as epidrugs: Mechanistic pathways and pharmacodynamic actions. Biomolecules. 2022;12(3): 367. https://doi.org/10.3390/biom12030367
9. Mohammad SI., Owida HA., Kumar R., Beemkumar N., Mahapatro A., Jacob A., Pant R. Effect of powder oxygen content on inclusion morphology and mechanical behavior of maraging steels processed by laser powder bed fusion. Applied Physics A, 2025;131(11): 1-14. https://doi.org/10.1007/s00339-025-09010-y
10. Owida HA., Mohammad SI., Vasudevan A., Bishoyi AK., RenukaJyothi S., Panigrahi R., Pargaien A. Kinesin superfamily proteins in cancer: unveiling their role in chemotherapy. International Immunopharmacology, 2025;166: 115621. https://doi.org/10.1016/j.intimp.2025.115621
11. Mohammad AAS., Mohammad SI., Vasudevan A., Alshurideh MT., Nan D. On the numerical solution of the Bagley-Torvik equation using the M\. Computational Methods for Differential Equations. 2025;13(3): 968-979. https://doi.org/10.22034/cmde.2025.65631.3029
12. Mohammad SI., Owida HA., Vasudevan A., Menon SV., Al-Hasnaawei S., Ray S., Ranjbar, F. Thermophysical properties of used frying oil biodiesels blended with alcohols: Robust machine learning frameworks for density prediction. Industrial Crops and Products, 2025;236: 121916. https://doi.org/10.1016/j.indcrop.2025.121916
13. Elkashty OA., Tran SD. Sulforaphane as a promising natural molecule for cancer prevention and treatment. Current Medical Science. 2021;41(2): 250-269. https://doi.org/10.1007/s11596-021-2341-2

14. Zafar S., Khan K., Hafeez A., Irfan M., Armaghan M., Rahman AU., Bagiu RV. Ursolic acid: A natural modulator of signaling networks in different cancers. Cancer Cell International. 2022;22(1): 399. https://doi.org/10.1186/s12935-022-02804-7
15. Jara M., Norlin J., Kjær MS., Almholt K., Bendtsen KM., Bugianesi E., Knudsen LB. Modulation of metabolic, inflammatory and fibrotic pathways by semaglutide in metabolic dysfunction-associated steatohepatitis. Nature Medicine. 2025;31: 1-13. https://doi.org/10.1038/s41591-025-03799-0
16. Rathee S., Patil UK., Jain SK. Exploring the potential of dietary phytochemicals in cancer prevention: A comprehensive review. Journal of Exploratory Research in Pharmacology. 2024;9(1): 34-47. http://dx.doi.org/10.14218/JERP.2023.00050
17. Fakhri S., Moradi S Z., Moradi SY., Piri S., Shiri Varnamkhasti B., Piri S., Bishayee A. Phytochemicals regulate cancer metabolism through modulation of the AMPK/PGC-1α signaling pathway. BMC cancer. 2024;24(1): 1079. https://doi.org/10.1186/s12885-024-12715-7
18. Tanaka T., Aoki R., Terasaki M. Potential chemopreventive effects of dietary combination of phytochemicals against cancer development. Pharmaceuticals. 2023;16(11): 1591. https://doi.org/10.3390/ph16111591
19. Mohammad AAS., Mohammad SIS., Al Oraini B., Vasudevan A., Hindieh A., Altarawneh A., Ali I. Strategies for applying interpretable and explainable AI in real world IoT applications. Discover Internet of Things. 2025;5(1): 71. https://doi.org/10.1007/s43926-025-00155-z
20. Mohammad AAS., Mohammad S., Al-Daoud KI., Al Oraini B., Vasudevan A., Feng Z. Building Resilience in Jordan's Agriculture: Harnessing Climate Smart Practices and Predictive Models to Combat Climatic Variability. Research on World Agricultural Economy. 2025;6(2): 171-191. https://doi.org/10.36956/rwae.v6i2.1628
21. Ding Y., Hou R., Yu J., Xing C., Zhuang C., Qu Z. Dietary phytochemicals as potential chemopreventive agents against tobacco-induced lung carcinogenesis. Nutrients. 2023;15(3): 491. https://doi.org/10.3390/nu15030491
22. Açar Y., Akbulut G. Nutritional epigenetics and phytochemicals in Cancer formation. Journal of the american nutrition association. 2023;42(7): 700-705. https://doi.org/10.1080/27697061.2022.2147106
23. Ionescu VS., Popa A., Alexandru A., Manole E., Neagu M., Pop S. Dietary phytoestrogens and their metabolites as epigenetic modulators with impact on human health. Antioxidants. 2021;10(12): 1893. https://doi.org/10.3390/antiox10121893
24. Mohammad AAS., Nijalingappa Y., Mohammad SIS., Natarajan R., Lingaraju L., Vasudevan A., Alshurideh MT. Fuzzy Linear Programming for Economic Planning and Optimization: A Quantitative Approach. Cybernetics and Information Technologies, 2025; 25(2): 51-66. https://doi.org/10.2478/cait-2025-0011
25. Mohammad AA., Al-Ramadan AM., Mohammad SI., Al Oraini B., Vasudevan A., Alshdaifat N., Hunitie MFA. Customer Sentiment Analysis for Food and Beverage Development in Restaurants using AI in Jordan. Data and Metadata, 4, 922-922. https://doi.org/10.56294/dm2025922
26. Shoaib A., Tabish M., Ali S., Arafah A., Wahab S., Almarshad FM., Rehman MU. Dietary phytochemicals in cancer signalling pathways: Role of miRNA targeting. Current Medicinal Chemistry. 2021;28(39): 8036-8067. https://doi.org/10.2174/0929867328666210420101605
27. Mohammad AAS., Mohammad SIS., Al-Daoud KI., Al Oraini B., Vasudevan A., Feng Z. Optimizing the Value Chain for Perishable Agricultural Commodities: A Strategic Approach for Jordan. Research on World Agricultural Economy. 2025;6(1): 465-478. https://doi.org/10.36956/rwae.v6i1.1571
28. Hussain Y., Khan H., Alsharif KF., Hayat Khan A., Aschner M., Saso L. The therapeutic potential of kaemferol and other naturally occurring polyphenols might be modulated by Nrf2-ARE signaling pathway: Current status and future direction. Molecules. 2022;27(13): 4145. https://doi.org/10.3390/molecules27134145
29. Mohammad AAS., Mohammad SI., Al-Daoud KI., Al Oraini B., Qurneh M., Vasudevan A., Wang Y. Digital Platforms and Agricultural Marketing: Bridging Gaps between Farmers and Consumers in Jordan. Research on World Agricultural Economy. 2025;6(3):740-756. https://doi.org/10.36956/rwae.v6i3.1570