REVIEW ARTICLE

The Association of Sugar and Sugar Substitutes to Breast, Lung, and Oral Cancer Cell Lines: A Scoping Review

Zainal M[a,c,d], Md Asri NS[a], Mohamed Faizal NS[a], Said Gulam Khan HB[a], Wan Ahmad Kamil WN[a,c,d], Mohd Sarmin NI[a], Mohd Kornain NK[b], Arzmi MH[c,d]*

[a]Faculty of Dentistry, University Teknologi MARA, Jalan Hospital, Selangor, Malaysia
[b]Faculty of Medicine, University Teknologi MARA, Jalan Hospital, Selangor, Malaysia
[c]Department of Fundamental Dental & Medical Sciences, Kulliyyah of Dentistry, International Islamic University Malaysia, Kuantan, Pahang, Malaysia
[d]Cluster of Cancer Research Initiative IIUM (COCRII), International Islamic University Malaysia, Pahang, Malaysia

ABSTRACT

Cancer which synonymously known as neoplasia is a genetic disorder of cell growth that is triggered by acquired or less commonly inherited mutations affecting a single cell and its clonal progeny. The aims of this scoping review was to investigate the role of sugar and sugar substitutes in breast, lung, and oral cancers with a hypothesis that sugar promoted carcinogenesis. Three databases (EBSCO, PubMed, and Scopus) were searched from January 2010 to December 2021 to identify the preclinical studies eligible for this scoping review. The review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) guidelines. A total of 361 articles were reviewed and the qualitative synthesis used 12 of these articles. Based on the qualitative synthesis, four studies reported dietary sugar (glucose- and/or sucrose) induced cancer progression, one study revealed sugar substitute (aspartame) induced cancer proliferation, seven studies reported that sugar substitutes inhibit cancer proliferation, and one study reported that sucrose promotes cancer while xylitol inhibits cancer. In addition., it was reported that D-allose and cisplatin have a synergistic effect in treating cancer. In conclusion, simple sugar intake is associated with an increased risk of carcinogenesis. In contrast, sugar substitutes inhibit cancer cell line progression, subsequently acting as a potential cancer therapy, thus supporting the study's hypothesis.

Keywords
Cancer risk factors, sugar, sugar substitutes, carcinogenesis

Corresponding Author
Dr. Mukarramah Zainal
Centre of Preclinical Science Studies,
Faculty of Dentistry, UiTM Sungai Buloh,
Jalan Hospital, 47000 Sungai Buloh,
Selangor.

E-mail : mukarramah@uitm.edu.my

Received: 1st July 2022; Accepted: 21st February 2023

Doi: https://doi.org/10.31436/imjm.v22i4

INTRODUCTION

Worldwide statistical cancer trends are rapidly growing.[1] Cancer is synonymously known as tumour or neoplasia. It is defined as a "genetic disorder of cell growth that is triggered by acquired or less commonly inherited mutations affecting a single cell and its clonal progeny".[2]

As reported by GLOBOCAN, breast cancer is ranked as the 1st most common cancer worldwide, followed by lung cancer. Meanwhile, oral cancer is ranked the 11th most common cancer worldwide.[3] Most of the oral cancer cases have been reported from Asian countries.[4] The majority of OSCC cases are identified at advanced stages.[5] Cancers are a broad group of complicated diseases that potentially metastasise.[6,7] The aetiology can either be inherited or acquired or both.[8,9] Acquired aetiology, such as diet, is a modifiable factor seen as a worthy target to be focused on to maximise cancer survival rate. Indeed, the worldwide cancer trend is expected to increase due to adopting an unhealthy lifestyle.[10,11]

The association between sugar and tumorigenesis remains unclear.[12] Fundamentally, cells require energy to maintain their integrity and growth. This energy is generated within mitochondria in the presence of substrate such as glucose through a biochemical process which eventually produces adenosine triphosphate (ATP).[13,14] Glucose is the simplest form of carbohydrates, a type of sugar that the body uses to produce energy. The dietary sugar consumed daily is a

source of cell-ATP supply.[15] However, natural sugar substitutes (SS) such as xylitol, erythritol, tagatose, and trehalose, and synthetic SS such as saccharin, aspartame, sucralose, and acesulfame potassium are the non-ATP source.[16]

Cancerous cells require a massive supply of ATP for biomolecule production.[13] Angiogenesis increases the delivery of energy fuels to the cells.[17] Therefore, high dietary sugar may spike the proliferation of cancerous cells.[13, 17] It is also suggested that carcinogenesis may be promoted by a high sugar diet, which stimulates the synthesis of insulin and insulin-like growth factor-I (IGF-I), inducing oxidative stress and promoting weight gain.[18] Other than the obesity and adiposity pathways, mechanisms underlying a link between sugary drinks and cancer might involve insulin resistance caused by their high glycaemic index, which has been related to breast cancer,[19] biliary tract cancer,[20] hepatocellular cancer,[21] and diabetes-related carcinomas.[22] In addition, various pathway has also been linked, which associate sugar and cancer, such as provoking inflammation cascade.[23]

Sugar-sweetened beverages (SSBs) are the most consumed caloric beverages and the driving source of added sugars.[24] It potentially increases the risk of obesity, which is perceived as a potent cancer risk factor. Studies have shown that sugar promotes cancer progression rather than cancer development.[25, 26] Aspartame, a synthetic SS found in fruit juices, might play a role in cancer development[27, 28]. Whilst in other articles showed contradictory results.[25]

Sugar consumption is rising worldwide, yet its definite association with cancer is mainly unknown.[18] A proper study is required to investigate the potential of sugar or SS to promote carcinogenesis. Evidence of the association between sugar and cancer risk in preclinical models has been acknowledged as a reliable tool to provide a clear answer with solid reasoning and justification.[29] Hence, a scoping review that properly summarised and synthesised all related evidence on sugars and their effect on cancer is needed.

This scoping review highlighted three types of cancer: breast, lung and oral cancer. The justification for selecting these cancers is to map, identify knowledge gaps and clearly describe the differences in indications between the top rank epidemiological cancer (breast and lung) research trend with less common cancer (oral cancer) on the impact of sugar and sugar substitutes on carcinogenesis potential. This study focuses on the cancer parameters assessing the DNA damage, cancer cell viability, and proliferation.

MATERIALS AND METHODS

The scoping review was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) guidelines (Figure 1). It aims to improve the quality of scoping review protocols, similar to the impact achieved by other reporting guidelines.[30]

Formulation of Review Question

The question of this scoping review was formulated according to the PICO formulation. PICO stands for the population of the studies (P), intervention or exposure (I), comparison of intervention or exposure (C), and outcome of the interest (O).[31] For the present study, PICO is formulated as follows where P: breast, lung, and oral cancer population, I: sugar and sugar substitute, C: the activity of the sugar and sugar substitute on the normal cell and cancer cell, and O: the effects of sugar and sugar replacement on the cancer cell. This formulation has been suggested in the Cochrane Handbook for Systematic Reviews for Interventions as a potential model for developing review questions and search terms.[32] Therefore, the formulated question for this review is "What are the effects of sugar and sugar substitutes against breast, lung, and oral cancer?"

Search strategy

Scopus, PubMed, and EBSCO were used throughout this scoping review. The articles were restricted to the English language. The search terms were set as [("in vitro" OR "tissue" OR "cells" OR "ex vivo" OR "animal") AND

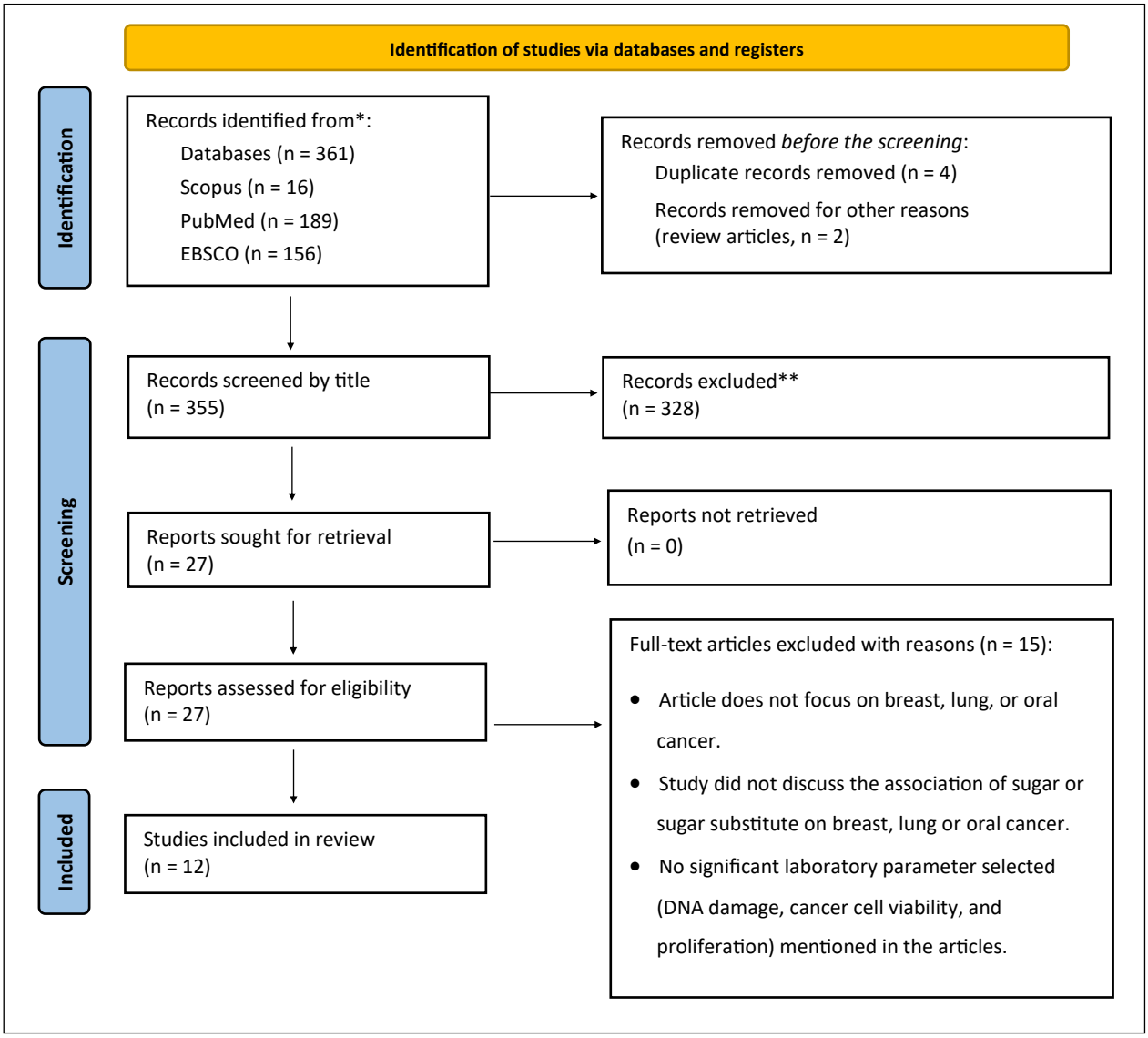

Figure 1: Flowchart of the data selection process in accordance with PRISMA-ScR guidelines.

("sugar" OR "artificial sugar" OR "artificial sweeteners") AND ("cancer" OR "breast cancer" OR "HER2" OR "MCF7" OR "MDA-MB-231" OR "lung cancer" OR "lung carcinoma" OR "oral cancer" OR "OSCC") AND ("DNA" OR "Comet Assay" OR "cell proliferation" OR "Ki-67" OR "MTT" OR "cell viability")]. The identical search strategy was applied in all databases. The search aimed to identify all randomised controlled trial studies design, which later, the effects of sugar and sugar substitutes on breast, lung, and oral carcinogenesis were summarised.

Eligibility Criteria

The inclusion criteria of this scoping review are (i) publication type is an original article with the criteria of implementing experimental research on the association of the sugar and sugar substitute with breast, lung, and oral cancer, and (ii) the article was published between January 2010 up to December 2021 and excluded the studies dated before and after, (iii) article was published in the English language, (iv) the studies is worldwide (no restriction to any region or country) and (v) the participants included in the published article are preclinical studies both in-vitro and in-vivo. Studies that did not

focus on PICO formulation were excluded from this review. Grey studies were also excluded. Case reports, letters, conference abstracts, and review papers were also excluded.

Data extraction

The three screening stages (title, abstract and full text) were done independently by four authors (NA, NF, MZ, and HS). Any disagreements were resolved by discussion among authors. The characteristics of the included studies in this review (author, year, country of study, type of study, samples, and laboratory methods), described the association of sugar to breast, lung, and oral cancer progression were analysed by (MZ, HS, WNH, and NIS) and summarised in Table I.

RESULTS

Studies included

Initially, 361 records (Scopus: 16, PubMed: 189, EBSCO: 156) were found from the database search. The studies were then checked for duplicates and article types, resulting in 355 potentially eligible studies for inclusion. The study titles and abstracts were screened to select relevant studies for inclusion in the review, leaving only 27 studies qualified for full-text screening. Only 12 studies were eligible to be included in the review based on the inclusion criteria. Kappa score among the authors showed a high level of agreement (K>0.90).

Study characteristics

All studies included in this scoping review discussed the association of sugar with cancer progression. Five studies were reported dietary sugars, namely glucose- and sucrose -induced cancer progression.[33-37] Whilst five studies revealed that sugar substitutes inhibit cancer proliferation, subsequently acting as potential cancer therapy.[38-43] However, a survey conducted by Alleva et al. 2011[44] showed a sugar substitute, aspartame-induced angiogenesis, indirectly promotes cancer proliferation. Another study reported the significant suppression proliferation of oral cancer upon xylitol or sucrose plus xylitol supplementation.[35] The synergistic effect of D-allose/cisplatin on cancer was also mentioned in a study.[39] The analyses of the articles were summarised in Table I.

The Association of Sugar with Cancer Progression and Proliferation

The association of sugar with cancer progression and proliferation depends on the types of sugar tested. In this scoping review, the selected paper eligible for analysis revealed glucose and/or sucrose induce cancer cell proliferation.[33 - 37] In contrast, two other studies revealed sucrose in combination with artificial sugar demonstrated anti-tumour effects against cancer progression and proliferation.[35,41] Regarding artificial sugar, the result showed cancer inhibition,[38 - 42] except for aspartame.[44] To evaluate the anti-tumour properties, apoptosis and cell proliferation assays were utilised. The laboratory output results showed good evidence, either quantitatively or qualitatively. This is a reliable experimental tool for observing apoptotic cell development and evaluating cell proliferation suppression.[40, 42, 43]

An in-vitro study reported the partial substitution of glucose by xylitol, a type of sugar alcohol, notably suppressed proliferation and ATP generation of oral cancer cells. Suggested that xylitol is likely to play a role in suppressing oral cancer development.[35]

Another study pointed out that particular sugar may elicit an anti-tumour effect in combination with existing anticancer drugs. This study revealed that D-allose, a rare monosaccharide inhibited non-small cell lung cancer (NSCLC) cell proliferation in-vitro and tumour growth in-vivo. Together with cisplatin, a widely available chemotherapeutic drug for lung cancer, D-allose synergistically possessed growth inhibitory potential in NSCLC, suggesting that the sugar could be a new supplement to treat lung cancer. D-allose showed a more significant anti-proliferative effect on squamous cell carcinoma than adenocarcinoma.[39]

A previous investigation demonstrated that polysaccharides from the marine alga *Gracilariopsis lemaneiformis* (PGL) inhibited cell proliferation, altered cell

Table I: Summary of studies assessing the Association of Sugar and Sugar Substitutes to Solid Tumours

Ref. no.	First Author, year	Title	Type of Study	Cell lines and sugar tested	Laboratorial Method	Impact on cancer cell line
(38)	Icsel et al. 2020	Trans-Pd/Pt (II) saccharinate complexes with a phosphine ligand: Synthesis, cytotoxicity and structure-activity relationship	In-vitro experimental study	• Cancer cell lines: Breast (MCF-7), and lung (A549) human cancer cell lines. • Normal cell line: BEAS-2B human bronchial epithelial • Tested sugar compound: Artificial sweetener (saccharinate) complexes • Control tested compound: Cisplatin	1.ATP method – cell viability assay 2.DNA binding 3.DNA groove binders 4.Molecular docking 5.Enzyme inhibition study 6.Cytotoxicity study	Inhibit the proliferation of cancer cell
(44)	Alleva et al. 2011	In vitro effect of aspartame in angiogenesis induction	In-vitro experimental study	• HUVEC, human umbilical vein endothelial cells • IMR-90, human cell line • Sugar tested: Artificial sweetener (aspartame)	1.In vitro angiogenesis assay (Angio-Kit model) 2.Cell viability assay (MTT) 3.Inflammatory mediator and growth factor determination 4.Intracellular ROS assay by flow cytometry (FACS) 5.Western blot analysis	Induce the proliferation of cancer cell
				PubMed (8 articles)		
(39)	Kanaji et al. 2018	Additive anti-tumour effect of D-allose in combination with cisplatin in non-small cell lung cancer cells.	In-vitro and in-vivo experimental study	• Cell culture: Human NSCLC cell lines (squamous cell carcinomas: EBC1 and VMRC-LCD; adenocarcinomas: A549, HI1017, and RERF-LC-A1, NCI-H1975) • Animals and xenotransplantation: EBC1 cells were inoculated into BALB/c-nu mice. • Sugar tested: Sugar (monosaccharide) D-allose • Drug used: Cisplatin		Inhibit the proliferation of cancer cell
(33)	Tchounwou CK, Yedjou CG, Farah I, Tchounwou PB. 2014	D-Glucose-Induced Cytotoxic, Genotoxic, and Apoptotic Effects on Human Breast Adenocarcinoma (MCF-7) Cells	In-vitro experimental study	• Cell culture: human breast adenocarcinoma (MCF-7) cells • Sugar tested: D-glucose	1. MTT assay 2. Comet assay 3. Flow cytometry	Induce the proliferation of cancer cell
(40)	Akter et al. 2015	A New Cytotoxic Steroidal Glycoalkaloid from the Methanol Extract of Blumea lacera Leaves.	In-vitro experimental study	• Normal cell line: NIH 3T3 (fibroblast cell) and VERO (epithelial cell) • Cancer cell line: MCF-7 and MDA-MB-231 • Sugar tested: Artificial sweetener (sugar moiety of analogous Steroidal Glycoalkaloid)	1. Cytotoxic assay (MTT) assay 2. Annexin V-FITC apoptosis assay 3. Flow cytometry - Cell cycle analysis	Inhibit the proliferation of cancer cell
(43)	Kang et al. 2017	Characterisation and Potential Antitumor Activity of Polysaccharide from Gracilariopsis lemaneiformis.	In-vitro experimental study	• Human non-small cell lung cancer (NSCLC) cell line A549 • Sugar tested: galactose	1. CCK-8 assays - Cell viability analysis 2. Annexin-FITC/PI Apoptosis analysis – Flow cytometry 3. Fas/FasL Expression Analysis – Quantitative Real-Time PCR (RT-qPCR) & NanoDrop 2000 spectrophotometer 4. Western Blot Analysis 5. siRNA and transfection 6. Cell Invasion and Migration Analysis	Inhibit the proliferation of cancer cell
(34)	Rao et al. 2015	O-GlcNAcylation of G6PD promotes the pentose phosphate pathway and tumor growth	In-vitro and in-vivo experimental study	• Normal cell lines: 293T, • Cancer cell lines: A549 (lung cancer), MCF7 (breast cancer), H661 (lung cancer), • Immunocompromised mice (BALB/c-nude, male, 5 - 6-week-old, Charles River Laboratories) • Sugar tested: N-acetylglucosamine	1. Bicinchoninic Acid protein assay 2. Modified coupled enzyme assay 3. Glucose Uptake Fluorometric Assay Kit 4. NADP+/NADPH Quantitation Kit 5. Glutathione Assay Fluorimetric Kit 6. Lactate dehydrogenase (LDH)-based toxicology assay kit 7. Cell proliferation assays	Induce the proliferation of cancer cell
(35)	Trachootham et al. 2017	Partial Substitution of Glucose with Xylitol Suppressed the Glycolysis and Selectively Inhibited the Proliferation of Oral Cancer Cells	In-vitro experimental study	Normal cell lines: 293T, Cancer cell lines: A549 (lung cancer), MCF7 (breast cancer), H661 (lung cancer), Immunocompromised mice (BALB/c-nude, male, 5 - 6-week-old, Charles River Laboratories) Sugar tested: N-acetylglucosamine	1. Bicinchoninic Acid protein assay 2. Modified coupled enzyme assay 3. Glucose Uptake Fluorometric Assay Kit 4. NADP+/NADPH Quantitation Kit 5. Glutathione Assay Fluorimetric Kit 6. Lactate dehydrogenase (LDH)-based toxicology assay kit 7. Cell proliferation assays	

Ref. no.	First Author, year	Title	Type of Study	Cell lines and sugar tested	Laboratorial Method	Impact on cancer cell line
(36)	Wong et al. 2020	The nutrient sensor OGT regulates Hipk stability and tumorigenic-like activities in Drosophila	In-vivo experimental study	• Fly (Drosophila) culture • Normal Cell lines: kidney epit helial cell (HEK293) • Cancer cell lines: Breast cancer cell (MCF-7) • Sugar tested: glucosamine, sucrose	1. Quantitative Real Time-PCR 2. Western blotting 3. Cycloheximide (CHX) Assay	Induce the proliferation of cancer cell
(37)	Eichenlaub et al. 2018	Warburg Effect Metabolism Drives Neoplasia in a Drosophila Genetic Model of Epithelial Cancer	In-vivo experimental study	• In-vivo: Drosophila melanogaster strains • Normal Cell lines: HTM3522 (breast epithelial cells) • Sugar tested: sucrose	1. RNA extraction and microarrays 2. Quantitative PCR 3. Immunostaining - anti-DE-Cadherin, anti-MMP1 4. LDHA expression 5. 3D Epithelial polarisation assay 6. Lactate measurement - Seahorse XF^{e}96 Extracellular Flux Analyzer	Induce the proliferation of cancer cell
			EBSCO (2 articles)			
(41)	Mondal et al. 2016	Evaluation of in vitro antioxidant, anticancer, and in vivo anti-tumour activity of Termitomyces clypeatus MTCC 5091	In-vitro and in-vivo experimental study	• In-vitro: Cancer cell lines: human breast carcinoma cell line (MDA-MB-468), human lung adenocarcinoma epithelial cell line (A549) • In-vivo: Xenograft Male Swiss albino mice • Sugar tested: sugar substitute consists of ascorbic acid, fructose, sucrose, arabitol, inositol, and traces of xylitol	1. Coomassie blue (Bradford) protein assay reagent 2. HPLC - Monosaccharide composition analysis 3. In vitro antioxidant assays 4. Ferrous ion-chelating (FIC) assay 5. ABTS radical cation decolorisation assay 6. MTT assay	Inhibit the proliferation of cancer cell
(42)	Shan et al. 2013	Triticuside A, a Dietary Flavonoid, Inhibits Proliferation of Human Breast Cancer Cells Via Inducing Apoptosis	In-vitro experimental study	• Cancer Cell lines: Human breast cancer (MCF-7, MDA-MB-231) • Sugar tested: sugar substitute flavonoid glucoside (glucose)	1. MTT cell viability assay 2. Clonogenicity assay 3. Apoptosis assay - Flow cytometric analysis of Annexin V/7-AAD staining 4. Western blot analysis - Bio-Rad DC assay reagent	Inhibit the proliferation of cancer cell

morphology, and promoted apoptosis in cancer cells, especially NSCLC cell line A549. Also, apoptosis induction is mediated by the Fas/Fas ligand (Fas/FasL) pathway, which plays a significant role in tumorigenesis.[43] A comparative experimental study in 2016 identified anticancer activity against a few cancer cells of the aqueous extract of Termitomyces clypeatus, an edible mushroom. This mushroom extract contained 31% protein, 32% carbohydrate, and 10-14% ascorbic acid with evidence of sugar entities when analysed with high-performance liquid chromatography (HPLC).[39] One study highlighted the importance of sugar moieties for the cytotoxic activity of steroid glycoalkaloids (SGAs) which induced apoptosis and cell cycle disturbance.[40] In comparison, another in-vitro experimental study revealed the cell proliferation inhibition of human breast cancer cells by *Triticuside A*, a flavonoid C-glycoside from wheat bran, via the mitochondrial apoptosis pathway as well as the Akt/mTOR signaling pathway.[42]

DISCUSSION

This scoping review provides evidence on the association of sugar with cancer progression and proliferation. The general theoretical hypothesis pathway of sugar promotes carcinogenesis is drawn in the diagram below.

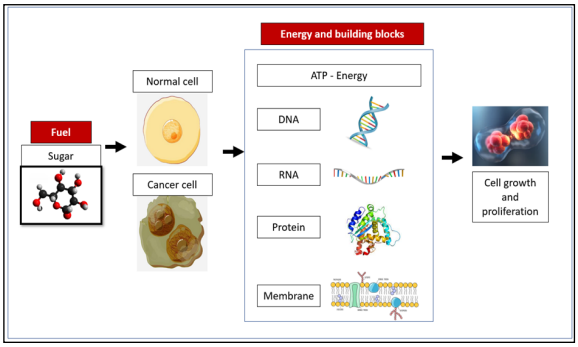

Figure 2: The sugar fuels in cancer biology. Cells, either normal or cancerous, can utilise sugar as their fuel. Sugar is taken up by cells, converted and processed to make molecules essential for providing the cell with energy (ATP) and also for generating molecules that contribute to the essential building blocks of macromolecules (DNA, RNA, and proteins) and form lipid bilayers for the configurations of membranes around cells which is vital for cell life. Therefore, these macromolecules are the building blocks that form the physical components of a cell. A cell that proliferates needs a lot of these macromolecules. Genomic information (RNA and DNA) is critical for cell growth and proliferation. Cells use sugar as fuel to generate energy and maintain homeostasis, and that's important to their specialised function. By contrast, cancer cells upregulate the fuel usage to make more of the macromolecules needed for the building blocks to make the cancer cell's mass and physical form. Ultimately it contributes to the growth and proliferation of the cancerous cell.

Sugar promotes cell proliferation

Some studies revealed natural sugar substitutes demonstrated anti-tumour effects against cancer progression and proliferation.[40] On the other hand, several studies showed a possible association between prolonged intake of heavy synthetic artificial sugar and cancer.[41, 42] The link between artificial sweeteners and cancer is still debated. A recent meta-analysis and case-control study discovered that artificial sweetener usage was not linked to

an increased risk of cancer when all types of cancers were analysed intensively except for urinary system cancer in women.[43]

In cancer cells, glucose metabolism shifts from using pyruvate to feed oxidative phosphorylation toward the use of lactate in aerobic glycolysis (the Warburg effect).[44] In the transition to Warburg metabolism, the lactate dehydrogenase enzyme is crucial. Cancer cells' growth is thought to be enhanced by diverting glucose to generate building blocks for increased biomass in the form of amino acids at the cost of ATP production efficiency through the tricarboxylic acid (TCA) cycle. Thus, the Warburg effect metabolism acts as a co-factor for the epidermal growth factor receptor (EGFR). A Drosophila model requires this growth factor for epithelial neoplasia and metastasis. This has been verified that lactate dehydrogenase (LDH) fuelled up neoplasia, and increased glucose consumption promotes neoplasia in the study.[37]

Another finding is an indirect link between sugar metabolism and cancer cell development. Aspartame (APM), a sugar substitute, stimulated blood vessel formation (angiogenic agent) at low supplementation doses. It induces regenerative cytokine production, leading to the activation of MAPKs and subsequently forming new blood vessels. The formation of new blood vessels from pre-existing capillaries (angiogenesis) is required for tumour development. Angiogenic signalling pathways are crucial in various diseases, including cancers, cardiovascular diseases, etc. The toxic effects of APM have been primarily based on its ability to cause cell transformation over the years. If a malignant cell has developed itself, it needs factors to help it evolve, supported by angiogenesis. On top of that, APM increases the levels of inflammatory mediator IL-6, VEGF, and their soluble receptors released from endothelial cells into the medium. This sugar substitute can induce VEGF-pathway activation by erk1/2 and p38 phosphorylation.[44]

Additionally, a study has shown that glucose consumption and cell proliferation indirectly relate to protein O-GlcNAcylation of glucose-6-phosphate dehydrogenase (G6PD and pentose phosphate pathway (PPP). An in-vitro enzymatic assay done by a previous study showed an increase of OGT (an enzyme responsible for adding O-GlcNAcylation onto proteins) activity in cell lysate under hypoxia[34]. Hypoxic therapy improved glucose uptake rate significantly, which was associated with an increase in O-GlcNAcylation level. As a result, O-GlcNAcylation of G6PD appears to accelerate cellular biosynthesis and induce cell proliferation.

The Association of Sugar with Cancer Induced-DNA Damage

The association of sugar with cancer-induced-DNA damage was investigated by Icsel et al., 2020.[38] In this experimental study, breast (MCF-7), colon (HCT116), and lung (A549) human cancer cell lines were used to evaluate the cytotoxicity of New trans-[Pd(sac)2(PPhMe2)(DMSO)]·H2O (Pd) and trans-[Pt(sac)2(PPhMe2)2]· H2O (Pt) complexes (sac=saccharinate and PPhMe2= dimethyl-phenyl phosphine) in-vitro. ATP viability assay was used, and it showed that Pd was biologically inert, whilst Pt showed significant anticancer potency on MCF-7 cancer cells, similar to cisplatin. Based on the results, Pt appeared to target DNA, while Pd had a higher affinity for human serum albumin (HSA). Pt activity mechanism studies revealed that apoptotic cell death was caused by a significant increase in intracellular ROS (reactive oxygen species) levels, mitochondrial damage, and the formation of DNA double-strand breaks.

To assess the complexes' DNA binding in-vitro, plasmid pBR322 DNA was incubated. The DNA cleavage ability and the amount of DNA forms were determined. Pd complex showed no DNA cleavage at low concentrations, but single-strand breaks (SSBs) on the plasmid DNA were observed at high concentrations. This tested configuration of the substitute sugar complex induces tumour single-strand DNA (ssDNA) damage. On the other hand, the Pt complex is more potent than the Pd complex since Pd at high concentration induces ssDNA while the Pt complex demonstrates a concentration-dependent DNA cleavage. This was confirmed when they performed a nuclease activity assessment; the nuclease activity of the Pt complex is much higher than the Pd complex.

DNA groove binder analysis was performed to assess DNA binding by investigating DNA cleavage or damage

upon exposure of plasmid pBR322 DNA to the DNA minor groove binders; DAPI (4',6-diamidino-2-phenylindole) and major groove binders; MG (methyl green). The results suggest that Pd and Pt complexes selectively bind to DNA's major groove.

The molecular docking method was used to analyse the *trans*-configured Pd and Pt complexes' DNA binding affinity. The docking data gained from the study showed the formation of strong NH···O hydrogen bonds between both complexes with the adenine moiety of DNA, as well as the construction of electrostatic interactions between the sac's phenyl ring and the oxygen of DNA's phosphate backbone. The binding energies of both Pd and Pt docked with DNA are higher than of cisplatin as the complexes bind to DNA non-covalently while cisplatin binds to DNA non-covalently.[45]

The findings from the study proposed that on several cancer lines, both *trans*-configured Pd and Pt complexes demonstrate different cytotoxic activity, with Pt being higher cytotoxicity than Pd, which is biologically inert.

CONCLUSION

Our scoping review revealed that dietary sugar could proliferate cancer cells model in-vitro through the production of ATP. Our findings also highlighted that sugar substitutes might potentially be an anti-tumour with cancer type-dependent, thus supporting the study's hypothesis.

LIMITATIONS OF THE STUDY

This study highlighted the scope within the in-vitro study model and covered three types of cancer: breast, lung, and oral. Therefore, further studies should be conducted on animals before a clinical trial involving humans to resemble the exact human pathophysiology of cancer.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We acknowledge all the team members as pioneers of the proposed work and backbone throughout the manuscript reviewed. This work was supported by DUCS 2.0 research grant: 600-UiTMSEL (PI. 5/4) (029/2020)

REFERENCES

1. Cancer [Internet]. [cited 2022 Jun 9]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cancer
2. Vinay Kumar; Abul K Abbas; Jon C Aster. Robbins & Cotran Pathologic Basis of Disease. 10th Edition. Turner JR, editor. Elsevier. Philadelphia, PA: Jeremy Bowes 2020.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 2018;68:394–424.
4. Farooq I, Bugshan A. Oral squamous cell carcinoma: metastasis, potentially associated malignant disorders, etiology and recent advancements in diagnosis. F1000Res [Internet]. 2020 [cited 2022 Jun 27];9. Available from: /pmc/articles/PMC7194458/
5. Hadzic S, GojkovVukelic M, Pasic E, Dervisevic A. Importance of Early Detection of Potentially Malignant Lesions in the Prevention of Oral Cancer. Mater Sociomed [Internet]. 2017 [cited 2022 May 30];29(2):129. Available from: https://pubmed.ncbi.nlm.nih.gov/28883777/
6. Cancer [Internet]. [cited 2021 Nov 24]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cancer
7. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209–49.
8. Wang JL, Chang CH, Lin JW, Wu LC, Chuang LM, Lai MS. Infection, antibiotic therapy and risk of colorectal cancer: A nationwide nested case-control study in patients with Type 2 diabetes mellitus. International Journal of Cancer 2014;135:956–67.
9. Tiffon C. The impact of nutrition and environmental epigenetics on human health and disease. International Journal of Molecular Sciences. MDPI AG 2018;19.

10. Goncalves MD, Hopkins BD, Cantley LC. Dietary Fat and Sugar in Promoting Cancer Development and Progression. Annual Review of Cancer Biology 2019;3:255–73.
11. Cancer Research UK. Sugar and cancer – what you need to know - Cancer Research UK - Science blog [Internet]. 2019 [cited 2020 Apr 29]. Available from: https://scienceblog.cancerresearchuk.org/2017/05/15/sugar-and-cancer-what-you-need-to-know/
12. Li Y, Guo L, He K, Huang C, Tang S. Consumption of sugar-sweetened beverages and fruit juice and human cancer: A systematic review and dose-response meta-analysis of observational studies. Journal of Cancer. Ivyspring International Publisher 2021:3077–88.
13. Kim SY. Cancer energy metabolism: Shutting power off cancer factory. Biomolecules and Therapeutics 2018:26;39–44.
14. Li Y, Guo L, He K, Huang C, Tang S. Consumption of sugar-sweetened beverages and fruit juice and human cancer: a systematic review and dose-response meta-analysis of observational studies. J Cancer 2021;12:3077–88.
15. Clarke, Margaret A. and Singh RP. Sugar | chemical compound | Britannica [Internet]. [cited 2021 Apr 9]. Available from: https://www.britannica.com/science/sugar-chemical-compound
16. Bukhamseen F, Novotny L. Artificial sweeteners and sugar substitutes -some properties and potential health benefits and risks. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2014;5:638–49.
17. Angiogenesis Inhibitors - National Cancer Institute [Internet]. [cited 2021 Nov 24]. Available from: https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/angiogenesis-inhibitors-fact-sheet
18. Toews I, Lohner S, Küllenberg De Gaudry D, Sommer H, Meerpohl JJ. Association between intake of non-sugar sweeteners and health outcomes: Systematic review and meta-analyses of randomised and non-randomised controlled trials and observational studies. BMJ 2019;364.
19. Chazelas E, Srour B, Desmetz E, Kesse-Guyot E, Julia C, Deschamps V, et al. Sugary drink consumption and risk of cancer: Results from NutriNet-Santé prospective cohort. BMJ 2019;366.
20. Larsson SC, Giovannucci EL, Wolk A. Sweetened Beverage Consumption and Risk of Biliary Tract and Gallbladder Cancer in a Prospective Study. J Natl Cancer Inst. 2016;108.
21. Schlesinger S, Chan DS, Vingeliene S, Vieira AR, Abar L, Polemiti E, et al. Carbohydrates, glycemic index, glycemic load, and breast cancer risk: a systematic review and dose-response meta-analysis of prospective studies. Nutrition Reviews V R 2017;75:420–41.
22. Laguna JC, Alegret M, Roglans N. Simple sugar intake and hepatocellular carcinoma: Epidemiological and mechanistic insight. Nutrients. MDPI AG; 2014;6:5933–54.
23. Della Corte KW, Perrar I, Penczynski KJ, Schwingshackl L, Herder C, Buyken AE. Effect of Dietary Sugar Intake on Biomarkers of Subclinical Inflammation: A Systematic Review and Meta-Analysis of Intervention Studies. Nutrients 2018;10.
24. Tasevska N, Jiao L, Cross AJ, Kipnis V, Subar AF, Schatzkin A, et al. NIH Public Access 2012;130:159–69.
25. Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I, et al. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomised controlled trial 1-4. Am J Clin Nutr. 2011;94:479–85.
26. Larsson SC, Giovannucci EL, Wolk A. Sweetened Beverage Consumption and Risk of Biliary Tract and Gallbladder Cancer in a Prospective Study. J Natl Cancer Inst. 2016;108:djw125.
27. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Meeting (2011 February 15-22 : Lyon F, International Agency for Research on Cancer. Some chemicals present in industrial and consumer products, food and drinking-water. International Agency for Research on Cancer 2013:586.
28. Alleva R, Borghi B, Santarelli L, Strafella E, Carbonari D, Bracci M, et al. In vitro effect of aspartame in angiogenesis induction. Toxicology in Vitro

2011;25:286–93.
29. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Vol. 144, Cell 2011:646–74.
30. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Annals of Internal Medicine 2018;169:467–73.
31. Eriksen MB, Frandsen TF. The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. J Med Libr Assoc. 2018;106:420.
32. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. Cochrane Handbook for Systematic Reviews of Interventions 2019:1–694.
33. Tchounwou CK, Yedjou CG, Farah I, Tchounwou PB. D-Glucose-Induced Cytotoxic, Genotoxic, and Apoptotic Effects on Human Breast Adenocarcinoma (MCF-7) Cells. J Cancer Sci Ther [Internet]. 2014 [cited 2022 Jan 25];6(5):156. Available from: /pmc/articles/PMC4264661/
34. Rao X, Duan X, Mao W, Li X, Li Z, Li Q, et al. O-GlcNAcylation of G6PD promotes the pentose phosphate pathway and tumor growth. Nature Communications [Internet]. 2015 Sep 24 [cited 2022 Feb 1];6. Available from: /pmc/articles/PMC4598839/
35. Trachootham D, Chingsuwanrote P, Yoosadiang P, Mekkriangkrai D, Ratchawong T, Buraphacheep N, et al. Partial Substitution of Glucose with Xylitol Suppressed the Glycolysis and Selectively Inhibited the Proliferation of Oral Cancer Cells. Nutr Cancer [Internet]. 2017 Aug 18 [cited 2022 Feb 1];69(6):862–72. Available from: https://pubmed.ncbi.nlm.nih.gov/28718681/
36. Wong KKL, Liu TW, Parker JM, Sinclair DAR, Chen YY, Khoo KH, et al. The nutrient sensor OGT regulates Hipk stability and tumorigenic-like activities in Drosophila. Proc Natl Acad Sci U S A [Internet]. 2020 Jan 28 [cited 2022 Feb 1];117(4):2004–13. Available from: https://www.pnas.org/content/117/4/2004
37. Eichenlaub T, Villadsen R, Freitas FCP, Andrejeva D, Aldana BI, Nguyen HT, et al. Warburg Effect Metabolism Drives Neoplasia in a Drosophila Genetic Model of Epithelial Cancer. Curr Biol [Internet]. 2018 Oct 22 [cited 2022 Feb 1];28(20):3220-3228.e6. Available from: https://pubmed.ncbi.nlm.nih.gov/30293715/
38. Icsel C, Yilmaz VT, Aygun M, Ulukaya E. Trans-Pd/Pt(II) saccharinate complexes with a phosphine ligand: Synthesis, cytotoxicity and structure-activity relationship. Bioorganic & Medicinal Chemistry Letters 2020;30:127077.
39. Kanaji N, Kamitori K, Hossain A, Noguchi C, Katagi A, Kadowaki N, et al. Additive anti-tumour effect of D-allose in combination with cisplatin in non-small cell lung cancer cells. Oncol Rep [Internet]. 2018 Mar 1 [cited 2022 Jan 28];39(3):1292–8. Available from: https://pubmed.ncbi.nlm.nih.gov/29328484/
40. Akter R, Uddin SJ, Tiralongo J, Darren Grice I, Tiralongo E. A New Cytotoxic Steroidal Glycoalkaloid from the Methanol Extract of Blumea lacera Leaves. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques [Internet]. 2015 [cited 2022 Feb 1];18(4):616–33. Available from: https://pubmed.ncbi.nlm.nih.gov/26626252/
41. Mondal A, Banerjee D, Majumder R, Maity TK, Khowala S. Evaluation of in vitro antioxidant, anticancer and in vivo anti-tumour activity of Termitomyces clypeatus MTCC 5091. Pharm Biol [Internet]. 2016 Nov 1 [cited 2022 Feb 1];54(11):2536–46. Available from: https://pubmed.ncbi.nlm.nih.gov/27225970/
42. Shan Y, Cheng Y, Zhang Y, Guan FQ, Sun H, Ren XC, et al. Triticuside A, a dietary flavonoid, inhibits proliferation of human breast cancer cells via inducing apoptosis. Nutr Cancer [Internet]. 2013 Aug 1 [cited 2022 Feb 1];65(6):891–9. Available from: https://pubmed.ncbi.nlm.nih.gov/23909734/
43. Kang Y, Wang ZJ, Xie D, Sun X, Yang W, Zhao X, et al. Characterisation and Potential Antitumor Activity of Polysaccharide from Gracilariopsis lemaneiformis. Marine Drugs [Internet]. 2017 Apr 1 [cited 2022 Feb 1];15(4). Available from: /pmc/articles/PMC5408246/

44. Alleva R, Borghi B, Santarelli L, Strafella E, Carbonari D, Bracci M, et al. In vitro effect of aspartame in angiogenesis induction. Toxicol In Vitro [Internet]. 2011 Feb [cited 2022 Jan 28];25 (1):286–93. Available from: https:// pubmed.ncbi.nlm.nih.gov/20837131/