REVIEW

A Concept Centric Synthesis Matrix Framework (SMF) on Application of Green Biomarkers in OSCC

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Abstract

Oral Squamous Cell Carcinoma (OSCC), a malignancy with highest mortality index & contemptible life has proclaimed 40%-50% of survival index from many years. One of the most crucial challenges of this malignancy are oral cancer interception, early detection&its prevention. Recent scientific findings have highlighted the emergence of Green Biomarkers that constitutes natural plant-based products with their specific bioactive dietary components & phytochemicals for detoxifying oral carcinogens, thereby aiding as an ideal chemopreventive agents &potential next generation predictive and prognostic biomarkers in oral cancer. Till date, few empirical studies have inferred a positive correlation of these phytochemicals in down regulating certain gene expressions in carcinogenetic cascade by modulating the epigenetic complex interplay of disease concatenation within a malignant cell. Discovering the specific role of these phytochemicals in carcinogenesis, can further define core concepts and tactic theories on selection of prompt bioactive dietary components as biological targets against malignant cells,hence contributing for its potential prognostic & predictive roles in oral cancer treatments. We performed a Synthesis Matrix Framework (SMF)with concept centric approach to comprehend the role of Curcumin, Tea polyphenols, Broccoli Seed &Sprout Extract (BSSE) and Ginger in OSCC with aim of synthesizing evidence-based studies to help readers to precisely spot the study outcomes for future scope. Moreover, this framework benefits the research scholars to haul in and scoop the knowledge gap in existing literature with ease of understanding the argument matrix & conceptual framework of each of the study designs,for future directions inadvanced research. This SMF could synthesize specific outcomes that can further help the readers to understand the significance & efficiency of these phytochemicals as chemotherapeutic agents in OSCC.

Keywords: Green Biomarkers, Oral Squamous Cell Carcinoma, Prognostic Biomarkers, Predictive Biomarkers, Green Chemopreventive Agents, Bioactive Dietary Components, Phytochemicals, Nutraceuticals, Curcumin, Ginger, Green Tea Extract & BSSE.

Introduction

Oral Squamous Cell Carcinoma/Oral cancer/OSCC has unveiled a static record of about 40%-50% of survival index from past many decades.[1] As per the International Agency for Cancer Research (IARC) &Global Cancer Observatory (GCO) Report 2020, the estimated deaths due to OSCC is approx. 377,713 cases worldwide, thus, securing the "Top 20"list of diseases with highest mortality & morbidity index.[2] In the current scenario, the overall quality of life in patients with OSCC, even after the currently available medical therapies i.e surgery, radiotherapy, chemotherapy, immunotherapy&/or combination therapy, is still unsatisfactory & detrimental. The low therapeutic efficiency & high toxicity of conventional treatment approaches demand for a new pristine interventional therapy involving much "safer & affordable approach" such as "Green Biomarkers".

Introducing Green Biomarkers can pave way for new innovative path breaking concept in oral oncology. Involving natural plant-based products, this biological molecule can open new avenues to target specific bioactive dietary compo-

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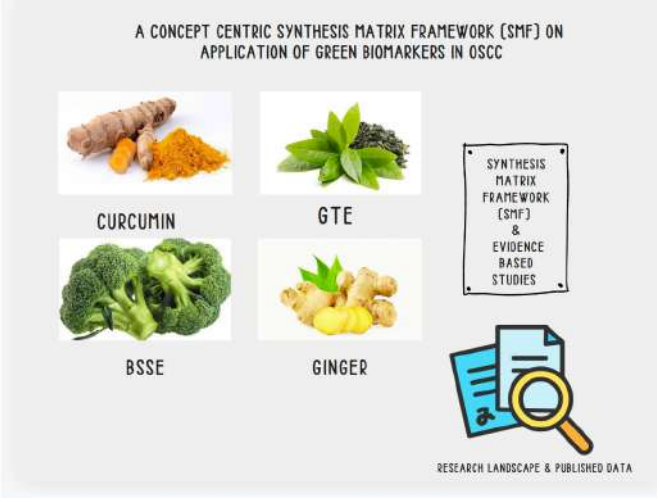
nents & phytochemicals for detoxifying oral carcinogens (benzene, aldehydes & polycyclic aromatic hydrocarbons), hence acting as an ideal chemopreventive agents in oral cancer. Various organizations such as World Health Organization (WHO), National Cancer Institute (NCI), the American Institute of Cancer Research (AICR), World Cancer Research Fund (WCRF), American Institute for Cancer Research (AICR) & European Prospective Investigation into Cancer and Nutrition (EPIC) have recommended daily consumption of these plant-based products, since it has proved to reduce the incidence rate of oral cancer. Discovering these phytochemicals with their specific role in oral carcinogenesis can further define core concepts and tactic theories on selection of prompt bioactive dietary components as biological targets against malignant cells, thereby revolutionizing the concept of Green Biomarkersin Oral Cancer. Till date, few empirical studies have inferred a positive correlation of these phytochemicals in down regulating certain gene expressions in carcinogenetic cascade by modulating the epigenetic complex interplay of disease concatenation within a malignant cell. The anticancer effect of these phytochemicals and bioactive components has largely been attributed in suppressing & inhibiting the activity of procarcinogens, regulating enzyme activity & scavenging free radicals, inhibiting protein folding in the endoplasmic reticulum & suppressing mutagenesis, detoxification by binding to specific compounds, differentiation & angiogenesis, preventing proliferation of malignant cells, enhancing apoptotic activity & evasion of immunosurveillance.

To the best of our knowledge, no studies have specifically addressed the level of efficiency &reversal role of green biomarkers in detoxifying oral carcinogens in various forms (smokeless/smoke) of tobacco consumption with its specific characterization of molecular targets in OSCC. Comparative analytical studies on correlation of these with immunohistochemical markers (IHC)was another grey area that needs future exploration. Research landscape & future recommendations should consider on studying the release profile index (RPI) of these biomarkers by assessing the pharmacokinetics, distribution and bioavailability to achieve maximum therapeutic potentials with minimum adverse effects. This review was conducted to address this knowledge gap in literature.

We performed a Synthesis Matrix Framework (SMF)with a concept centric approach to comprehend the role of Curcumin, Tea polyphenols, Broccoli Seed and Sprout Extract (BSSE) and Ginger in OSCC with aim of synthesizing evidence-based studies to help readers to precisely spot the study outcomes for future scope. Moreover, this framework benefits the research scholars to haul in and scoop the knowledge gap in existing literature so as to plan & execute more empirical studies involving human trails. Application of this framework delve with benefits of understanding the argument matrix (AI) & conceptual framework of each of the study designs, for future directions in advanced research. Before initiating this framework, a compendious & panoptic literature on the terminologies & hypothetical mechanism of green biomarkers in carcinogenesis have been mapped for the basic understanding of their enigmatic role in OSCC.



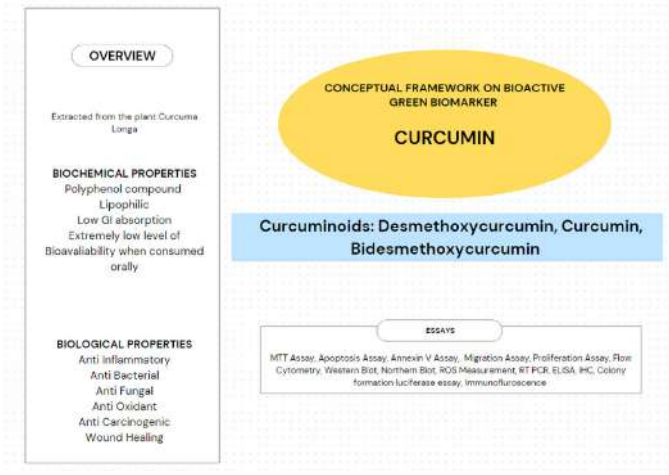


Fig. 1: Biochemical and Biological Properties of the Green Biomarker — Curcumin

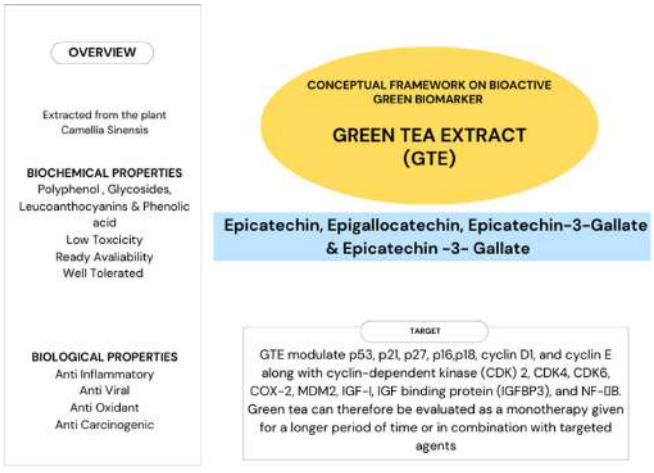


Fig. 2: Biochemical and Biological Properties of the Green Biomarker — Green Tea Extract

Definition/ Terminology

Green Biomarkers are defined as "natural biological molecules present on whole plant foods or their extracts that demonstrate cancer prevention activity". This concept was first introduced by Dr Jed Fahey and Dr Thomas Kensler in 2012. The incorporation of diet rich in plant-based products with their specific bioactive dietary components & phytochemicals have served as an effective interventional therapy in treatment of various cancers such as colorectal cancers, prostate cancers and adenomas.[3] The conceptualization of the word "Green" is derived for being sustainable as these biomarkers are environmental friendly, safe, natural, renewable & healthy source of intervention, thereby reducing the potential biohazards in health sciences. The term "Chemoprevention" implies a novel approach to arrest/reverse cancer using dietary bioactive natural/synthetic products for its suppression, reversal, or prevention from premalignant stage to malignant stage.[4] These bioactive dietary ingredients/ phytochemicals are also referred to Nutraceuticals i.e any food ingredient that provides medical and health benefits.[5] The enduring popularity of these nutraceuticals in recent years can be explained by the potential tendency of these micronutrients in acting slowly with minimal toxic side effects when compared to other therapies. Being a broader category, green biomarkers are a part of nutraceuticals in health sciences that serve as healthy source of intervention in carcinogenetic process. The tremendous potential of these bioactive components to increase the sensitivity of cancerous cells towards cellular damage and activation of apoptotic pathways is the main mechanism of action of natural plant based products. Latest advancements & new technologies including combinatorial synthesis and high-throughput screening have increased drug discovery platform using natural plant-based products.

Mechanism of Action (Theoretical Hypothesis)

Based on the core concepts & tactic theories, the hypothesis proposed for this novel concept was based on Green Chemoprevention as a promising approach for early cancer interception & prevention. The micronutrients present in certain food groups play a "protective role" in carcinogenetic cascade by acting as anti-oxidants, anti-inflammatory, anti-tumorigenic & apoptotic agents leading to reduction in free reactive radicals (ROS), DNA repair mechanism, regulation of lipid peroxidation and reduced glutathione (GSH), increased enzymatic activity for detoxifying carcinogens, epigenetic modulation/methylation of DNA methyl transferases (DNMT) & histone deacetylase (HDAC), down-regulation of genes expression related to epithelial mesenchymal interaction (EMT) process of carcinogenesis etc, thereby stating that consumption of these specific food groups can prevent oral cancer incidence. However, they failed to document the authoritative attribution of either the efficiency or reversal role of each specific bioactive dietary molecule/ingredient present in these food in oral carcinogenesis. Moreover, the presence of thousands of phytochemicals in these food components have shown to have "cancer preventive properties" such as stimulating the immune system, detoxifying the carcinogens, promoting DNA repair, inhibiting cancer cell proliferation, inducing apoptosis and regulating genetic-epigenetic pathways in carcinogenesis.[6] This led to the evolution of Green Biomarkers as a preventive strategic goal in cancer therapy to study the role of bioactive dietary components/ phytochemicals in different food groups, thereby encouraging increased consumption of these foods in cancer cases. Discovering these phytochemicals can aid as potential next generation predictive & prognostic biomarkers in oral cancer. However, many challenges have to be addressed in standardization and selection of variables such as selection of prompt bioactive food

Fig. 3: Biochemical and Biological Properties of the Green Biomarker — BSSE

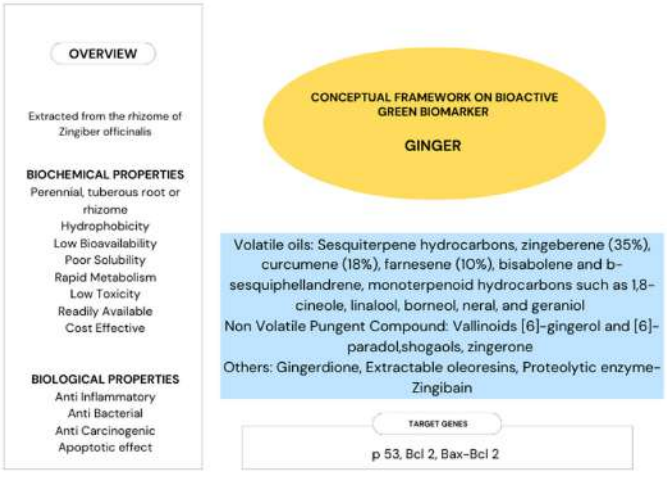


Fig. 4: Biochemical and Biological Properties of the Green Biomarker — Ginger

groups, dose & duration, mode of delivery i.e release profile index (RPI) and characterization of specific molecular targets for detoxifying carcinogenic potential in oral cancer cases.

Several studies in the past have already documented the causal symbiotic relationship between diet and oral cancer, thereby proving diet as one of the determinant etiological factor in oral carcinogenesis. These studies have inferred that individuals with low fibre intake and with the habit history of tobacco/ alcohol have high incidence of oral cancer. The enigmatic mechanism of action involves the interconnective role of both micronutrients and phytochemicals present in each food group wherein the complex mixture of these multiple compounds enhances the anti-carcinogenic effect in humans. E.g.: One plant food component acts as detoxifying agent and other plant component acts as antiproliferative agent, thereby indicating that regular consumption of mixed diet containing different food groups in balanced dose can prevent cancer.[7-10]

Applying this concept along with nutrition precision-based medicine in oral cancer can help to discover new phytochemi-

Table 1: SMF 1 of Evidence based studies on the role of green biomarker Curcumin in OSCC. The framework involves rows and columns. Each row represents Source information (SI) element time centred (Year of Publication), Role Centred (Author, Source/ Citation) & Outcome of Each Paper. The column represents the Argument Matrix (AM) element[17-23]

ARGUMENT MATRIX ELEMENT (AM)	"SMF FRAMEWORK 1"		
	SOURCE INFORMATION ELEMENT (SI)		
	Year	References	Study Outcome
Efficiency of green biomarker Curcumin & its components (Curcumin, Desmethoxycurcumin & Bisdesmethoxycurcumin) in detoxifying oral carcinogens in oral cancer with its enigmatic role in carcinogenesis. The level of efficiency in detoxifying oral carcinogens in various forms of tobacco usage with different modes of application (oral application, oral consumption and blood /salivary level analysis) needs to be explored	2020	Tang W et al[17]	The efficiency & oral bioavailability of curcumin is enhanced by combination of curcuminoids with essential oil of turmeric
	2020	Arun P et al[18]	Curcumin has an epigenetic role by modulating DNA methylation, histone modifications and miRNA expression in various human cancers by inducing apoptosis and inhibiting proliferation, migration, invasion and metastasis
	2020	Mishra A et al[19]	An analytical study conducted using curcumin in HPV associated Oral Cancer cell lines inferred morphological changes, decreased viability, E 6 mediated P53 downregulation, inhibition of NF-κB and AP-1
	2014	Xiao C[20]	An observational study using Curcumin on oral cancer cell lines inferred that it induces the expression of miR9, which mediates the inhibition of SCC9 cell proliferation and also inhibits the Wnt/ κcateninsignaling pathway
	2014	Zhen L[21]	An in vitro study conducted using curcumin in oral cancer cell lines inferred inhibition of SCC cell proliferation, down regulation of MMP 2, MMP 9, uPA and uPAR expression & cell cycle arrest at G2/M phase
	2011	Liao S[22]	An RT PCR study conducted using curcumin in oral adenosquamous cell carcinoma cell lines inferred the anticarcinogenic property such as apoptotic activity, growth inhibition, downregulation of NOTCH / Wnt Pathway, BCL 2, MMP 9, VEGF & Cyclin D1
	2006	Lao CD[23]	When 10 to 12 g of curcumin is taken orally, the maximum concentration in blood plasma is about 50.5 - 57.6 ng/ml, thereby proving its extremely low bioavailability property that is mostly eliminated from the body without being absorbed, thereby inferring the efficiency of oral bioavailability is comparatively less and needs other modes of administration.
Inferences derived:	A total of seven evidence-based studies on human trails of OSCC were synthesised for assessing their research outcome in which the role of curcumin and its apoptotic activity with inhibition of cell proliferation involving the epigenetic level in oral cancer cells was already been analysed. Future research needs to be conducted to assess the ***level of efficiency of Curcumin in detoxifying the oral carcinogens in all forms of tobacco usage with inclusion of basic lab investigation parameters applying blood and /or saliva.***		

cals and their bioactive components in food, thereby leading to the discovery of "Green Biomarkers" in oral cancer. Being categorized as an ideal chemopreventive agents, these natural food products are said to be non-toxic & cost effective with no side effects. Hence, this food centred strategic approach can be easily implemented in low & middle income countries by policy makers and educationalist for better outcomes in oral cancer cases.[11-13]

In the present review, we have included the role of four Green Biomarkers i.e Curcumin, Green Tea Extract (GTE), Broccoli Seed & Sprout Extract (BSSE) & Ginger in Oral Carcinogenetic process. The most common mode of action amongst these selected plant based biomarkers included the apoptotic pathway mechanism wherein the specific bioactive ingredient involved in each of these green biomarkers induced apoptosis, thereby inhibiting the progression of tumour cells with subsequent prevention of invasion & metastasis.

Curcumin:

Curcumin, referred as Diferuloylmethane, is extracted from the plant "Curcuma Longa". Three major class of bioactive components are present in curcumin namely Curcumin, Desmethoxycurcumin & Bisdesmethoxycurcumin. Numerous preparations of Curcumin have been developed to evaluate its curative & preventive properties as therapeutic agents in management of various human diseases. Scientific evaluations of curcumin have revealed several biochemical properties & biological properties as depicted in Figure 1.[14-16] The anti-cancer effect of curcumin is by inducing apoptosis and suppression of cellular signalling pathways by causing inhibition of proliferation and invasion of tumours, thereby preventing different phases of cancer like angiogenesis, progression & metastasis. Studies using preclinical models on human trails (systematic vs oral application) have concluded that curcumin preparations are safe with outstanding beneficial effects as shown in Table 1.[17-23]

Green Tea Extract (GTE):

The beneficial effects of GTE on human health have been documented in recent years. Derived from the plant "Camel-

Table 2: SMF 2 of Evidence based on role of green biomarker Green Tea Extract (GTE) in OSCC. The framework involves rows and columns. Each row represents Source information (SI) element time centred (Year of Publication), Role Centred (Author, Source/ Citation) & Outcome of Each Paper. The column represents the Argument Matrix (AM) element[26-28]

ARGUMENT MATRIX ELEMENT (AM)	"SMF FRAMEWORK 2"		
	SOURCE INFORMATION ELEMENT (SI)		
	Year	References	Study Outcome
Efficiency of green biomarker Tea Polyphenols & its components (Epicatechin, Epigallocatechin, Epicaechin-3-Gallate &Epigallo-catechin-gallate) in detoxifying oral carcinogens in OSCC with its enigmatic role in carcinogenesis.	2019	Belobrov S et al[26]	An observational study was conducted to assess the effect of green tea in oral cancer cell lines that inferred a strong association of epigallocatechin gallate (EGCG) bioactive component in inhibiting malignant cell proliferation & invasion, decreasing the expression of phosphorylated EGFR, thereby resulting in OSCC prevention
The level of efficiency in detoxifying oral carcinogens in various forms of tobacco usage with different modes of application (oral application, oral consumption and blood /salivary level analysis) needs to be explored	2007	Reiko Ide et al[27]	A prospective cohort study conducted in Japanese population inferred no association of green tea and inverse relationship in oral carcinogenesis, however, it showed reduced risk of oral cancer in subjects who consumed 5 to 6 cups of green tea per day especially in women
	2002	Li N et al[28]	An RCT study conducted on oral intake of Green Tea Extract (GTE) along with application of curcumin has shown to prevent oral cancer by its antitumor effects in 7,12, dimethylbenzanthracene, thereby acting as synergistic growth inhibition effect
Inferences derived:	A total of three evidence-based studies were assessed for the role of green tea extract (GTE) in oral cancer inferring its strong association of epigallocatechin gallate (EGCG) bioactive component in cessation of cell proliferative mechanism in oral carcinogenesis. Future research needs to be conducted to assess the level of efficiency of GTE in detoxifying oral carcinogens and its characterization of specific molecular targets with different modes of application (oral application, oral consumption and blood /salivary level analysis) in different forms of tobacco usage and its efficiency on reversal role in premalignant lesions/ OPMD's.		

lia Sinensis", this polyphenolic compound has four major class of bioactive components: Epicatechin (1-3%), Epigallocatechin (3-6%), Epicaechin-3-Gallate (3-6%) & Epigallo-catechin-gallate (3-7%). It constitutes about 36% of dry tea leaf weight. Other principal components of GTE are glycosides, leucoanthocyanins & phenolic acid. GTE preparations take various forms & its medicinal ingredients are normally extracted from dried leaves. The biochemical, pharmacological and biological prop-

Table 3: SMF 3 of Evidence based on role of green biomarker on BSSE & OSCC. The framework involves rows and columns. Each row represents Source information (SI) element time centred (Year of Publication), Role Centred (Author, Source/Citation) & Outcome of Each Paper. The column represents the Argument Matrix (AM) element[30-34]

ARGUMENT MATRIX ELEMENT (AM)	"SMF FRAMEWORK 3"		
	SOURCE INFORMATION ELEMENT (SI)		
	Year	References	Study Outcome
Efficiency of green biomarker BSSE & its components (sulforaphane or glucoraphanin (GR) in detoxifying oral carcinogens in OSCC with its enigmatic role in carcinogenesis. The microvascular density (MVD) and angiogenetic activityin malignant cellsneeds to be explored	2015	Cancer Genome Atlas N. H. (ude.cnu.dem@seyah), J. R. G. (ude.cmpu@rjsidnarg), A. E. N. (gro.nosrednadm@raggana).[30]	The bioactive dietary component present in broccoli is Sulforaphane that activates NRF2 signalling in HNSCC cell lines. The mechanism of preventive effects of sulforaphane are due to NRF2-mediated detoxication, prevention of tumour initiation and/or progression, or induction of apoptosis.
	2014	Egner PA et al[31]	A pilot study was conducted among healthy human volunteers in China to evaluate the bioavailability and pharmacodynamic efficiency of Broccoli seed extract preparation with defined concentrations of sulforaphane or glucoraphanin for 12 week exposure timeline. The study results inferred that BSE consumption of 70 μmolsulforaphane-equivalent by volunteers could prove sustained detoxification of air borne pollutants and carcinogens present in tobacco smoke.
	2006	Pavia M et al[32]	A systematic review conducted to synthesize epidemiologic studies on association of diet rich in Broccoli (cruciferous family) in oral cancer has inferred reduced risk of HNSCC & SPTs
	1997	Kensler TW et al[33]	This authors concluded that the cytoprotective activity mechanism of enzymes present in cruciferous vegetables such as Broccoli played a vital role in detoxifying the oral carcinogens such as benzene, aldehydes and polycyclic aromatic hydrocarbons
	1992	Prochaska HJ et al[34]	This study developed a system for rapid detection of enzymes present in diet that can detoxify oral carcinogens. Brocoli (SAGA) was one of the components involved. The phenomena of xenobiotic metabolism & detection of inducers of anticarcinogenic enzymes in human diet especially quinone reductase [NAD(P)H:(quinone-acceptor) oxidoreductase, EC 1.6.99.2]identified crucifers (and particularly those of the genus Brassica) as singularly rich sources, thereby conferring the hypothesis that high consumption of cruciferous vegetables has reduced risk of cancer in humans.
Inferences derived:	A total of five studies were synthesised and assessed for their specific role in detoxifying the oral carcinogens and study outcomes inferred the apoptotic role in oral carcinogenesis. Future research needs to be conducted to assess theangiogenetic effects of this bioactive dietary ingredient so as to counter effect the microvascular density (MVD) and angiogenetic activity in neoplastic tissue.		

erties of GTE are depicted in Figure 2.[24-25] The anticancer effect of GTE is by changing the expression of specific genes, downregulation of proinflammatory cytokines and mediating immune modulation mechnaism, thereby inducing cellular respone & apoptosis. Emerging scientific evidences have claimed GTE to be safe to consume with anticarcinogenetic properties in OSCC (Table 2).[26-28]

Broccoli Seed & Sprout Extract (BSSE)

Belonging to the Brassica genus of family of Cruciferous variety, this green biomarker contains bioactive dietary food component, sulforaphane or glucoraphanin (GR), that act as detoxifying agents of oral carcinogens. The detoxification efficiency of BSSE, when consumed orally, is measured by urinary excretion of glutathione-derived conjugates of acrolein, crotonaldehyde, and benzene, proving its anticarcinogenic effect. [29] The several biochemical & biological properties of BSSE are depicted in Figure 3. The anticancer effect of BSSE is by neutralization of free radicals by participating in various cellular reactions and enhancing the detoxification/purification of unwanted compounds, thereby improving immune health & body composition. Empirical meta-analytical studies have suggested that BSSE ameliorates anti carcinogenetic effect by apoptosis and/or anti proliferative mechanism. Data obtained from these studies are depicted in Table 3.[30-34]

Ginger:

Ginger (Zingiber officinale Roscoe, family: Zingiberaceae) is one of the oldest spice and herb with medicinal benefits. Being perennial plant, it has tuberous root and oblique round stem and is usually consumed orally as dry powder or paste or syrup in most of the countries. Its volatile compound, non-volatile pungent phenolic compounds & other constituents have many beneficial effects with chemopreventive effect on head and neck carcinoma. The biochemical & biological properties of Ginger are depicted in figure 4. Gingerol & Shogaols are considered to be the most active bioactive component against cancer. The anticancer effect of ginger is galteration in carcinogen-metabolizing enzymes, cell cycle arrest, and induction of apoptotic cell death and suppression of oncogenic signal transduction pathways. Studies have claimed that consumption of ginger boosts the immune system. However, more definitive link/hypothesis between ginger and its allied health benefits in oral cancer needs to be established. Evidence based studies on Ginger and oral cancer are depicted in Table 4.[35-36]

Research Landscape & Published Data:

Current workflows of published data comprise of animal studies involving heterogenous protocols and small sample size. The results underpin the need for more human trail prospective studies to evaluate the efficiency of these biomark-

Table 4: SMF 4 of Evidence based on role of green biomarker on Ginger & OSCC. The framework involves rows and columns. Each row represents Source information (SI) element time centred (Year of Publication), Role Centred (Author, Source/Citation) & Outcome of Each Paper. The column represents the Argument Matrix (AM) element [35-36]

ARGUMENT MATRIX ELEMENT (AM)	"SMF FRAMEWORK 4"		
	SOURCE INFORMATION ELEMENT (SI)		
	Year	References	Study Outcome
Efficiency of green biomarker Ginger & its components in detoxifying oral carcinogens in OSCC with its enigmatic role in carcinogenesis.	2012	Arshad NM et al [35]	An animal study was conducted to assess use of 1'S-1'-acetoxychavicol acetate (ACA), a component of Malaysian ginger alone or in combination with cisplatin (CDDP), in mice and the result showed apoptotic property that was measured using PARP and DNA fragmentation assay, cytotoxic effects by constitutive activation of NF-κB through suppression of IKKα/β activation &proinflammatory effects through NF-κB and COX-2, thereby reducing the tumor volume in OSCC
Future exploration of ginger in human trial studies needs to be explored on large scale	2010	Suresh K et al [36]	This animal study was conducted to evaluate (6)-paradol on 7,12-dimethylbenz(a)anthracene (DMBA)-induced hamster buccal pouch by measuring specific parameters such as the status of tumor incidence, volume and burden, phase II detoxification agents, lipid peroxidation and antioxidants. The study result inferred that (6)-paradol has potent chemopreventive, anti-lipid peroxidative and antioxidant potentials as well as a modulating effect on phase II detoxification enzyme and reduced glutathione (GSH) in DMBA-induced hamster buccal pouch carcinogenesis
Inferences derived:	A total of two animal studies were assessed to evaluate the role of ginger in OSCC and study outcome inferred the apoptotic role of ginger in oral carcinogenesis. Future research needs to be conducted to assess the level of efficiency of ginger in OSCC by conducting human trails on large scale.		

ers as adjunct interventional therapies in comprehensive oral cancer treatment. The concept centric approach of synthesis of the included studies inferred the apoptotic role as one of the major mechanisms to counteract and detoxify carcinogens (Table 1- 4). However, the angiogenetic activity needs to be explored as these dietary components can act as a double-edged sword wherein, they can act as provider of essential nutrients for the growth of malignant cells & inhibitor of carcinogenetic process through epigenetic shutdown mechanism. The studies also highlighted the need to update the knowledge on role of these biomarkers in reversing the carcinogenetic process from malignant stage to premalignant stage. Due to the complexity of methodology involved, these studies failed to document the release profile index (RPI) of these biomarkers & its level of efficiency including specific parameters such as pharmacokinetics, distribution and bioavailability in different forms of tobacco consumption in OSCC.

Future perspectives & Challenges:

Introducing Green Biomarkers in OSCC can be one of the innovative path breaking concept in oral cancer research as these are naturally available food components that are safe and easily available. Despite beneficial findings of potential role of Green Biomarkers in treatment of OSCC, several challenges need to be encountered. Studies needs to be conducted on evaluating the bioavailability data, long term toxicity and enhanced permeability- retention effects (EPR) of each green biomarker. Biosafety with FDA approval should be considered before conducting ongoing clinical trials using these biomarkers. A special consideration for studying the release profile index (RPI) of the green biomarkers needs to be identified as research gap and future experiments should illustrate its beneficial effects for offering maximum therapeutic potentials and reduced adverse effects by assessing its level of efficiency using specific parameters such as pharmacokinetics, distribution and bioavailability. Future research on correlation of green biomarkers with IHC markers can give clear concepts of efficiency levels of detoxifying effects of oral carcinogens and its benefits for early intervention.

Conclusion

Over the yester years, a lot of interest has been evoked to study the green chemoprevention concept of discovering new phytochemicals and its role in detoxifying the carcinogenic effects of oral cancer carcinogens that can be further conned for finding natural green biomarkers in OSCC. Tremendous interest has been created to know the enigmatic pathogenetic mechanism on how the bioactive dietary components are able to detoxify the carcinogens and downregulate certain gene expressions of carcinogenesis process, thereby modulating the functions of malignant cell and reducing the incidence of oral cancer. This SMF review is an attempt to cover four bioactive dietary components with comprehensive coverage of evidence-based studies on the same.

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