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Review

Bioactive compounds and their libraries: An insight into prospective phytotherapeutics approach for oral mucocutaneous cancers

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ABSTRACT

Oral mucocutaneous cancers (OMCs) are cancers that affect both the oral mucosa and perioral cutaneous structures. Common OMCs are squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and malignant melanoma (MM). Anatomical similarities and conventions which categorizes these lesions blur the magnitude of OMCs in diverse populations. The burden of OMC is high in the sub-Saharan Africa and Indian subcontinents, and the cost of management is prohibitive in the resource-limited, developing world. Hence, there is a pressing demand for the use of cost-effective in silico approaches to identify diagnostic tools and treatment targets for diseases with high burdens in these regions. Due to their ubiquitousness and accessibility, the use of therapeutic efficacy of plant bioactive compounds in the management of OMC is both appropriate and plausible.

Abbreviations: OMC, Oral mucocutaneous cancer; SCC, Squamous cell carcinoma; BCC, Basal cell carcinoma; MM, Malignant melanoma; FDA, Food and Drug Administration; NCCIH, National Center for Complementary and Integrative Health; NCI, National Cancer Institute; HPLC, High-performance liquid chromatography; GC-MS, Gas Chromatography Mass Spectrometry; TLC, Thin layer chromatography; MS, Mass spectrometry; NMR, Nuclear magnetic resonance; COX-2, Cyclo-oxygenase-2; COPD, Chronic obstructive pulmonary disease; HT-1, Hepatorenal tyrosinemia-1; D2, Dopamine receptors; Hsp90, Heat shock protein 90; PI3K, Phosphoinositide 3-kinase; PKB, Protein kinase B; MAPK, Mitogen-activated protein kinase; NF-κB, Nuclear factor kappa B; IL-8, Interleukin 8; IL-6, Interleukin 6; TNFα, Tumor necrosis factor-alpha; AMPK, AMP-activated protein kinase; EGFR, Epidermal growth factor receptor.

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Furthermore, screening known mechanistic disease targets with well annotated plant bioactive compound libraries is poised to improve the routine management of OMCs provided that the requisite access to database resources are available and accessible. Using natural products minimizes the side effects and morbidities associated with conventional therapies. The development of innovative treatments approaches would tremendously benefit the African and Indian populace and reduce the mortalities associated with OMCs in the developing world. Hence, we discuss herein, the potential benefits, opportunities and challenges of using bioactive compound libraries in the management of OMCs.

1. Introduction to bioactive compound libraries and product synthesis

The traditional use of in-vitro physical screening of large bioactive compound libraries for drug discovery is laborious and is being replaced by computer-aided virtual approaches, albeit the structural diversity and biological activities of natural product are inimitable [1]. Bioactive compound libraries are families of natural products and can be defined as a collection of pre-certified, functionally diverse structures, obtained from different natural sources, that have a wide range of applications [2]. Chemical reactions that are well-characterized are employed to create these highly valuable set of library compounds from easily available monomers, from which library compounds can be designed using a combinatorial approach [3]. However, high-quality screening of large bioactive compound libraries for RNA or protein in an unbiased way was a limitation of combinatorial chemistry; and the "rise and fall of combinatorial chemistry" has resulted in an increased use of in-silico virtual compound libraries [4]. Furthermore, the lack of specificity of the bioactive compound in therapeutic targeting of cellular/subcellular sites, fraught their routine uses [5].

These libraries include a vast array of products such as, natural products, pioneering compounds, approved compounds, and clinical compounds [6]. They can also be used for signal pathway research, drug discovery and drug repositioning [7]. Bioactive compounds are of immense importance in the management of various medical conditions/diseases, including cancer [8]. These natural compounds, which are largely isolated from microorganisms, plants and animals are bioactive and exert pharmacological effects in the treatment of human pathologies. Furthermore, these bioactive compounds can be used as nanocarriers for drug-delivery due to their superior biocompatibility, as compared to synthetic nanoparticles [8]. Virtual phenotypical screening of bioactive compound libraries is a cost-effective, seamless and plausible approach to the discovery of drug targets in human diseases. Although, these compound libraries present a treasure trove of targeted therapies for various medical conditions, their use has been poorly explored in the field of dentistry and oral pathology, particularly in oral mucocutaneous cancers (OMCs). Hence, this review seeks to discuss the application of natural and virtual compound libraries in the management of common OMCs viz: basal cell carcinomas (BCC), malignant melanomas (MM) and squamous cell carcinomas (SCC). Currently, there are six major orthodox therapeutic interventions for mucocutaneous cancers viz; surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, Bone marrow/stem cell transplant and hormone therapy. Despite progress made with these interventions, the use of natural bioactive compounds and compound libraries has a tremendous complementary benefit as an ancillary tool for OMC cancer management.

2. Physical natural product libraries and products

Several microbes, animals and plants with bioactivity can be candidates for the compound library development (Fig. 1). Various parts of plants such as stem, root, leaf, fruit and flower as well as microbial cultures are also vital sources for bioactive compound extraction using various approaches such as, molecule distillation, membrane separation, ultracentrifugation and enzyme-mediated extraction techniques. The products obtained are then safely stored in Natural Compound Libraries which are employed for drug discovery applications. These bioactive compound libraries have certain features in common as enlisted below:

- All necessary safety measures to ensure safety and bioactivity of natural extracts are established by various preclinical and clinical trials.
- All the important details of natural compound, for instance- chemical structure, physical properties, IC_{50} value etc., are reported.
- Bioactive compounds or extracts provided by these libraries are used in research work concerned with drug discovery for various diseases such as neurological disorders, cancer, cardiac disorders etc.

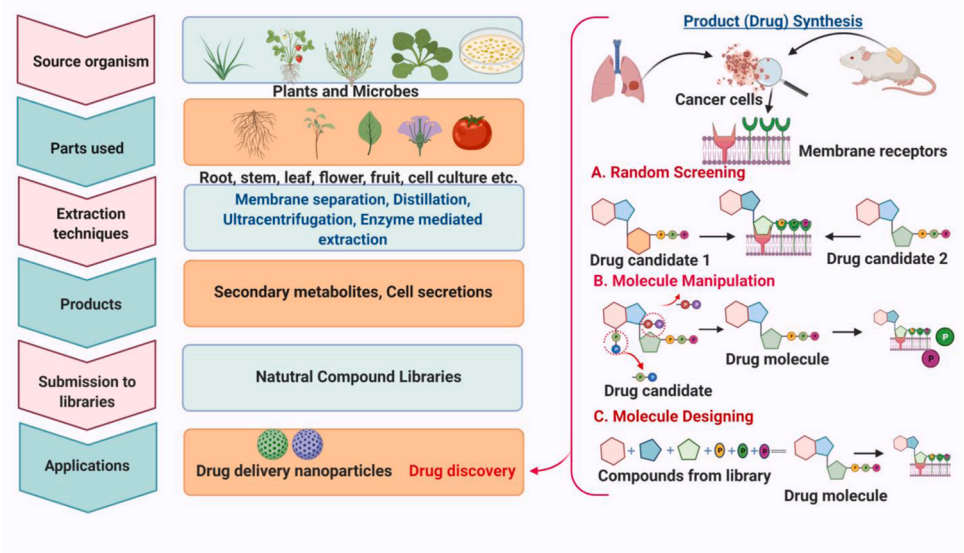

Fig. 1. Natural Compound Libraries and Product. *Explanatory notes*: Various plants and microbes with medicinal properties can be used as a source for the extraction of drug candidates. Root, stem, leaf, flower, fruits and microbial cell cultures are the starting materials that are subjected to different extraction techniques such as, membrane separation, molecule distillation, ultracentrifugation, enzyme mediated extraction techniques. Products obtained through these techniques are stored/kept safe in Natural Compound Libraries. These compounds from Natural Compound Libraries are used for various applications including drug discovery and synthesis. (Created with www.BioRender.com).

- Apart from therapeutic effects, these compounds are actively used in various sectors such as agrochemicals, nutraceuticals, cosmetics, antimicrobials and insecticides manufacturing.
- The phyto-compounds available in these natural product libraries are used in discovery of drugs with low toxicity.
- These compounds or extracts are provided with prior approval by FDA.
- To confirm the accessibility of diverse bioactive compounds, these libraries are *ad infinitum* rationalized.

A list of such libraries of natural products has been supplied by National Center for Complementary and Integrative Health (NCCIH) which serves principle idea to provide relatively comprehensive information (see Table 1). These biocompound libraries include natural as well as synthetic extracts not only from plants but from fungus, insects and other organisms also.

The successful execution of a precedential pipeline for efficient natural products depends on organized compilation of natural raw extracts. The most prevalent and diverse library for screening of natural extracts was evolved in the 1980's and 1990's by the National Cancer Institute (NCI) [9]. An enormous number of specimens and cultures from diverse natural sources were processed by NCI and other cancer research

Table 1
List of various libraries providing natural product extracts.

	Name of the Library/ Service provider	Date of Establishment	Founder/ CEO/ Managing Director	Headquarters/ Office	Web-address	Materials/Information/Data Available in the Library
1.	Albany Molecular Research Inc.	1991	Thomas E. D'Ambra	Albany, New York, USA	https://www.amriglobal.com/	Natural products obtained from marine and terrestrial microbes and plants
2.	Biosortia Pharmaceuticals	2012	Ross O. Youngs	San Diego, California, United States	https://www.biosortia.com/	Highly defined natural products extracted unswervingly from in-situ source i.e., aquatic micro biome.
3.	Caithness Biotechnologies Ltd	2015	Clett Erridge	Leicester, United Kingdom	http://caithnessbiotechnologies.com/	Inimitable focus on specific plants with medicinal properties. Risk management through dietary epidemiology. Endeavor to exploit accessibility of natural compound libraries. Approximately 800 extracts are available in DMSO, microplate format.
4.	ChromaDex®	1999	Frank L. Jaksch	Los Angeles, California, United States	https://www.chromadex.com/	Extensive medley of high-quality Natural Products/Compounds along with references. Appropriate for the Industries associated in the midst of food and beverages, pharmaceutical and cosmetic souk.
5.	Cyano Biotech	2004	Dan Kramer	Berlin, Germany	http://www.cyano-biotech.com/	Provide natural compounds obtained from cyanobacteria.
6.	Developmental Therapeutics Program	1955	NCI, NIH	USA	https://dtp.cancer.gov/	One of the comprehensive compilations of natural products.Natural compounds are extracted from different microorganisms and plant sources present all over the world.It also includes Library of Medicinal Plant Extracts from China.
7.	Greenpharma	2000	Philippe Bernard	Orléans, France	https://www.greenpharma.com/company/	Miscellaneous purified natural compounds from numerous sources like bacteria, plants etc.
8.	INDOFINE Chemical Company Inc.	1981	Kotesarama Bezwada	New Jersey, USA	http://www.indofinechemical.com/	This company is concerned with providing herbal and dietary products.
9.	InterBioScreen	1997	Dr. Kartsev	Chernogola, Russia	https://www.ibscreen.com/	Synthetic and natural compounds along with their derivatives from natural sources including plant, fungus, insects, marine organisms etc.
10.	InterLink Biotechnologies	1991	Dr.Garcia-Lazcano	Princeton, New Jersey, USA	http://www.interlinkbiotech.com/	Microbial and plant extracts.
11.	Magellan BioScience	1997	John M. Cronan	Tampa, Florida, United States	http://www.magellanbioscience.com/	Extracts from invertebrates and plants.
12.	MicroSource Discovery Systems Inc.	1993	John Devlin	New Milford, CT, US	http://www.msdiscovery.com/	Collection includes alkaloids, flavanoids, sterols, diterpenes, benzophenones, and coumarins.
13.	Natural Products Discovery Institute	2011	Merck and Company	California,USA	https://www.scripps.edu/support-us/natural-products/	Microbial fermentations, plant sources, raw and partitioned extracts
14.	NatureBank	2015	James Tansey	Vancouver, Canada.	https://www.naturebank.com/	Marine and plant derived products such as enhanced extract, fraction as well as pure compounds.
15.	Quality Phytochemicals	2000	Song Gao	New Jersey, USA	http://www.qualityphytochemicalsllc.com	PurifiedPhyto-chemicals or natural compounds
16.	Selleck Chemicals	2009	Dean Henry	Texas, United States	http://www.selleckchem.com	Purified natural products for research
17.	Sequoia Sciences	1999	Gary Eldridge & Mark O'Neil-Johnson	Seattle, Washington, USA	https://sequoiasciences.com sequoia@sequoiasciences.com	Drug-like compounds isolated from plants and other sources that aid in developing new drug targets for various diseases.
18.	Specs	1987		Kluyverweg, Netherlands	https://www.specs.net/	Natural products and byproducts from plants, fungi, bacteria, and marine organisms.
19.	Target Molecule Corp.				https://www.targetmol.com/	Purified natural compounds like Alkaloids, Flavonoids, Phenols etc, obtained from plant, animal and microbes.
20.	TimTec	1995	Dr. Murat Niyazymbetov	Newark, Delaware, USA	www.timtec.net	Compounds obtained from plants, bacteria, fungus, and animal sources.

Abbreviations: NCI, national cancer institute; NIH, national institute of health

institutes to produce a huge collection of natural extract which was originally designed to assist the discovery of anti-cancer drugs [10]. Today, although it is non-essential to combine several organisms to acquire new bioactive molecules, likelihoods of accomplishment are meticulously allied with the choice of unambiguous assortments and the extent of unique samples. This can be achieved by maximizing the variety of natural products in bioactive compound libraries organized from microbes, plants, marine organisms and additional materials, provided the biodiversity, state, region or taxonomic group is well characterized.

Assembly of natural extracts with biomedical applications could be restricted to a specified group or *genera* or particularly designed bioactive compounds; for instance, allowing the study of a sequence with the help of given scaffold types [11]. In some laboratories, assessments of a few hundred natural biomedical compounds in different sets are common in exhaustive studies, also these small collections are easy to manage [12]. Nevertheless, to enhance the likelihoods of obtaining novel natural bioactive compounds from composite mixtures, the speedy initial step such as high-performance liquid chromatography (HPLC) or solid phase extraction is required for the enriching of natural raw materials [13]. Such operations can perk up further bio-chemical screening procedures. Additionally, these compounds can be identified faster with high throughput screenings, using emerging state-of-the-art mass spectrometry and omics technologies [14].

3. Bioactive compounds for cancer and Omics approaches

Biological research has revolutionized with the commencement of omics era, that enables the expansion of high-end technology for the attainment and analysis of the large available datasets [15]. This all-inclusive approach is poised to determine and comprehend novel patterns and possesses a wide range of applications that are important in the arena of biotechnology.

Over past decade, expanding public and private inquisitiveness and investments in cancer research have augmented the prospects to generate evidence, and assemble large quantities of data to comprehend cell death processes under biological conditions [16]. Multi-omics approach for cancer treatment integrates multiple omics methods (such as genomics, transcriptomics, proteomics and metabolomics) for the production and analysis of huge chemotherapeutic natural product data [17]. Out of many, the utmost promising breakthrough of omics biotechnology is the extensive identification of plant-based bioactive compounds.

For the past several years, biologists have been using genomics in almost all aspects of life, and the number of genomic resources in phyto-chemicals has now become progressively more significant [18]. One of the foremost restrictions on the usage of these resources for the development of cancer related techniques is the scarcity of complete online databases where complete information related to plant genome is available [19]. Comparative genomics of different groups of plants can help in identifying the genetic basis of desirable traits; in addition, the genetic composition accountable for the specified phenotype will facilitate the practice of genetic engineering in improving the cancer therapeutic sector [20].

Numerous transcriptomes have been vigilantly interpreted and considered, providing an exceptional stance into the miscellaneous transcription-related processes operating in plants [21]. Taking into consideration the great therapeutic significance of phyto-chemicals, the transcriptomic scheme has been applied in order to disclose the genetic pathways liable for pathogenesis and provide viable therapeutic targets in different type of cancers [21]. Both transcriptomics and genomics alone are insufficient to comprehend the multifaceted biology of phytochemicals and ought to be harmonized through proteomic and metabolomics approaches, inter alia.

Proteomics explains the processes involved in biological mechanism and their functions and also provides information of protein including the pre- and post-transcriptional modifications.as well as protein-protein interactions [22]. Plant metabolites also have unique therapeutic properties and stages of their biosynthesis dependent on genetics and environmental changes [23]. A full-scale investigation of plant metabolites is described as metabolomics [24]. Almost all plants with medicinal values yield a scarce variety of secondary active metabolites that are different from compounds documented in other plants, as they have distinct metabolic patterns that are highly interconnected with the distinctive features of their landscapes, which contain an example of continuous variation in physical parameters such as light, pressure, nutrients etc. [25]. The desired plant metabolites having great interest in cancer drug discovery are acknowledged and investigated in a targeted way, and usually, the quantity of metabolites isolated is miniscule. For high throughput metabolite profiling, ancillary techniques such as mass spectrometry (MS) and nuclear magnetic resonance (NMR) are essential [26].

In recent years, omics approaches have been endowed with new opportunities to recognize and illustrate high-value bioactive compounds from plant origin that are effective against OMCs [27]. However, exploring the discovery of therapeutic phyto-chemicals, involves the use of poorly annotated data bases, inadequate reference datasets, and a dearth of committed software. Regardless of declining expenses on omics approaches, the datasets accessible are still insufficient for relative tools to work proficiently and additional investments into the gathering of data from plant species is crucial. Therefore, integrative multi-omics approaches will eventually accelerate the discovery of reliable cancer drugs in various plant species [28].

The bioactive elements entrenched in plants have been the precursors of modern research into natural product research and are a major source of drug carrier molecules [29]. Synergistic integration of bioinformatics and omics data (transcriptomics, physiognomics, proteomics and metabolomics) could be utilized to explore and evaluate natural compound's mechanisms, in a more precise way. Emerging omics technologies allow the multiplexing and parallel processing of proteomics and metabolic data [30]. In addition, an evidence-based integration of modern biomedical tools and traditional medicine practices can remarkably transform new drug development strategies, leading to precision and personalized medicine for the treatment of several type of cancers including OMCs. Bioinformatics provides information on diseases, toxicity issues, treatment factors, etc. [31].

4. Biomedical applications of bioactive compounds

It is well-known that in primeval times, people used nature to accomplish their elementary requirements including usage of natural products as medicines for various diseases. Indeed, an archeological study has provided information that about 50,000 years ago, Neanderthals were acquainted with therapeutic values of medicinal plants and used them for remedial purposes [32]. Apart from ancient uses, the most primitive written chronicles of medicinal plants have been found in Mesopotamia, 2600 BCE, unfolding the practice of using some gymnosperms like cedar besides medicinal oils intended for treating certain conditions like cough, inflammation and fever [33]. Interestingly, the people of this region as well other parts of the world still practice using these plant parts and their ingredients as medicines [34]. Nowadays, approximately 70–95% of the residents in developing countries of Asia and Africa uses traditional medicine for the treatment of various ailments [35].

Phyto-chemicals and plant-derived products are hopeful options meant for improving clinical effectiveness of cancer patients and reducing adverse reactions [36]. Most of these phyto-chemicals are natural active chemicals carrying high anticancer properties [37]. The development of high-quality anticancer drugs with enviable effects commences with testing of natural extracts to detect antitumor activity trailed by isolation of active phyto-chemicals following in vitro and in vivo results as shown in Fig. 2 [38]. Various bioactive compounds extracted from different regions of plants have been identified for the

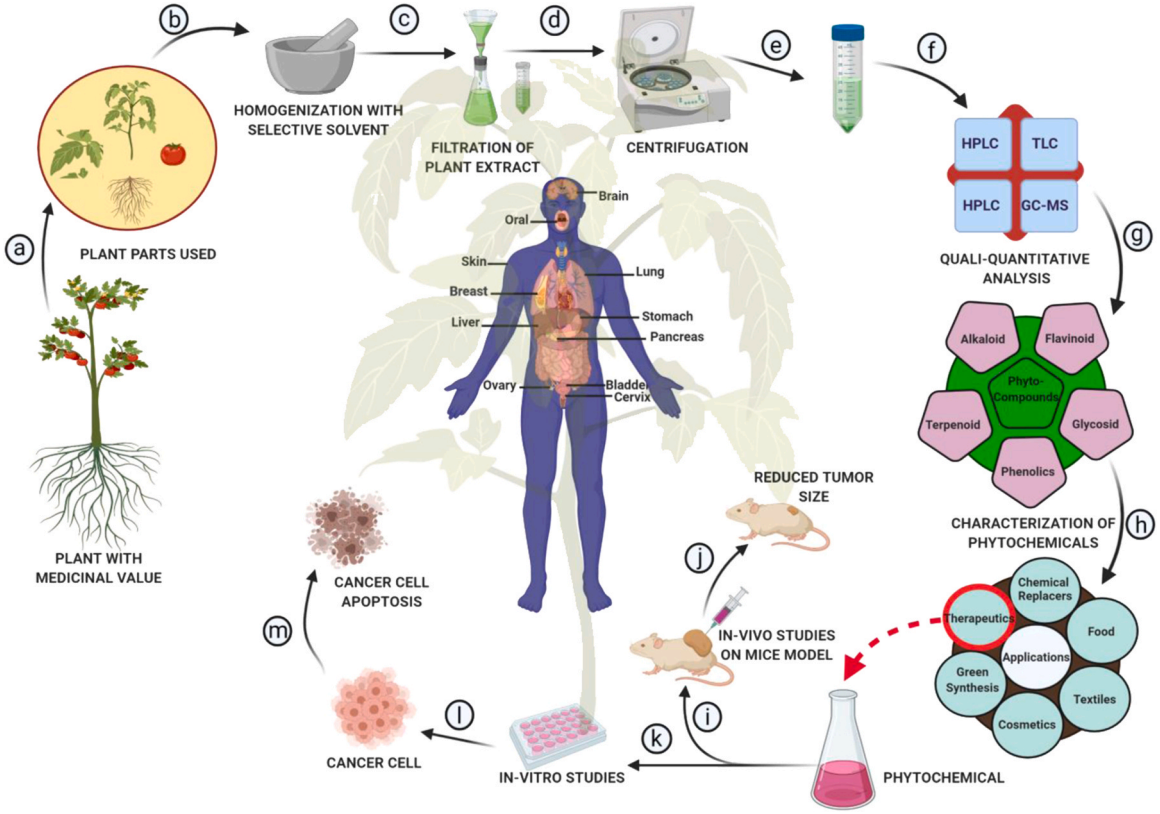

Fig. 2. Extraction of bioactive phyto-chemicals and their applications. *Abbreviations:* HPLC, high-performance liquid chromatography; TLC, thin layer chromatography; GC-MS, gas chromatography mass spectrometry. *Explanatory notes:* a. Selection of plant with medicinal properties and Isolation of plant parts to be used for extraction of bioactive compound b. Homogenization of plant part is carried out by using appropriate solvents. c-d. Homogenized extracts are subjected to filtration and centrifugation to obtain pure plant extracts e-f. Qualitative cum quantitative analysis of the Phyto-chemicals through various techniques such as HPLC, TLC, GC-MS etc. g. Characterization of obtained Phyto-chemicals into different groups h. Applications of Phyto-chemicals i-m. In-vivo (on xenografts) and in-vitro studies to check therapeutic potential of bioactive compounds obtained from plants (Created with www.BioRender.com).

treatment of human pathologies (Table 2). As depicted by many studies inhibition of COX-2 by Apigenin results in anti-inflammatory activity [39]. Also, use of Berberin hinders mitochondrial functions of target cells and can be used as a therapeutic prospective against numerous disorders [40]. Cryptolepine extracted from *Cryptolepis sanguinolenta* inhibits DNA synthesis showing cyto-toxic activity against malarial parasite [41]. Curcumin and Epigallocatechin-3- gallate isolated from different source plants are well known for their anti-cancer properties [] (42,43). Gossypol an extract isolated from ***Gossypium*** acts as an ant fertility agent by thwarting enzymes that are involved in energy providing metabolic reactions in spermatocytes [44]. Antiproliferative, antioxidant and cytotoxic activity of Linalool, Lycopene and Piperine include inhibition of dehydrogenase enzyme, quenching singlet oxygen and inhibition of the activity of EGFR tyrosine kinase enzyme.respectively [](45,46). Quercetin works as an anti cancer agent by block the PI3K / AKT pathway leading to a reduction in the expression of anti-apoptotic protein, thus acting as an anti cancer agent [47]. Apart from these, bioactive compounds such as Resveratrol, Sesquiterpene Coumarins, Sesquiterpenoids, Ursolic acid, Withaferin A, Apomorphine etc., have been validated for their efficacy in various diseases including cancer [53]. Arteether is used as an antimalarial agent as it inhibit the nutrient flow to erythrocytic stage of *Plasmodium falciparum* by modifying properties of membranes [54]. Galantamine, an alkaloid extracted from ***Galanthus woronowii*** is exploited for the treatment of Alzhemer as it escalates acetylcholine neurotransmission [55]. ***Callistemon citrinus*** extracts causes obstruction in the catabolic pathway of tyrosine that leads to a decline in the accumulation of venomous metabolites in Hepatorenal tyrosinemia [56]. It has been observed that Paclitaxel mediates anti cancer activity through endorsing arrest of mitosis and cell death [57]. Leaf and root extracts of ***Atropa belladonna*** have been found effective against asthma and chronic obstructive pulmonary disease by acting on specific muscarinic receptors located in the respiratory tract [58].

Many of these plants are endemic to the African and Asia continent and their use to ameliorate the increasing burdens of OMC cancers. In these regions that constitute a high percentage of the global low- and middle-income countries, should be explored.

5. Bioactive plant compounds for the management of OMC cancers

Cancer is major causes of death across the globe and owing its ubiquity the recognition of new anti-cancer remedies is imperative. The previous century has made prodigious strides in plant research and phytochemicals field, through admittance of numerous anti-cancer natural compounds already included in treatment practices [59]. A list of commercially accessible plant derived bioactive compounds for treating numerous cancers has been provided in Table 3, along with details like their source plant, plant family, plant part used for extraction of compound, type of studies (in-vitro/in-vivo) performed so far.

Several thriving anti-cancer drugs used in the therapeutics, revealed to be very efficient, are invented as natural products like microbes, plants and marine organisms [60]. Current developments in proteomics along with metabolomics have proven imperative for identification of novel therapeutic targets that proffer innovative therapeutic ideas. Most of the molecules with medicinal properties which were identified in the late 90 s and early 2000s, are natural products or their derivatives, utterly substituting antitumor agents [61]. In this perception, natural

Table 2
Biomedical Applications of Plant Derived Bioactive Compounds.

	Bioactive compound/ Natural product	Category/ Chemical nature	Origin/source plant	Plant family	Plant part used	Mechanism of action	Biomedical application	References
1.	Apigenin	Flavonoid	***Salvia officinalis***	Lamiaceae	Whole plant	Inhibition of COX-2 results in anti-inflammatory activity.	Antioxidant, anti-inflammatory, anti-mutagenic, antibacterial and antiviral properties	[39]
2.	Berberin	Alkaloid	***Coptis chinensis***	Ranunculaceae	Roots	Inhibit the function of mitochondria, prompt glycolysis and commencement of AMPK pathway.	Therapeutic prospective against numerous disorders (Cardiac disorders, Neurological disorders and Diabetes) Antibacterial, Anti-inflammatory, Cyto-toxic activity	[40]
3.	Casticin	Flavonoids	***Artemisia annua***	Asteraceae	Fruits	Expression of Bax protein is up regulated and Bcl-2 protein expression is down-regulated that results in arrest of the cell cycle at G2/ M phase and induce apoptosis.	Anti-proliferation, Inhibit self-renewal of hepatic stem cells, Anti-inflammatory	[76]
4.	Cryptolepine	Alkaloids	***Cryptolepis sanguinolenta***	Apocynaceae	Roots	Cyto-toxic activity of drug is as a result of inhibition of DNA synthesis.	Cyto-toxic activity, Antimalarial, Anti-plasmodial activity	[41]
5.	Curcumin	Polyphenols	***Curcuma longa***	Zingiberaceae	Rhizome	Initiation of apoptosis Obstruction of nuclear factor-kappa B (NF-κB) instigation Downregulation of numerous pro-inflammatory cytokines (IL-8, IL-6, and TNFα)	Anti-cancer Anti-inflammation Anti-angiogenic Antioxidant, and anti-mutagenic effects	[42]
6.	Epigallocatechin-3- gallate (EGCG)	Polyphenols	***Camellia sinensis***	Theaceae	Dried leaves	Antioxidan Drug resistance reversal	Antioxidative activity Anti-cancer DNA-protective Neuroprotective effect Anti-HIV	[43]
7.	Gingerol	Guaiacols	***Zingiber officinale***	Zingiberaceae	Rhizome	Inhibition of NF-κB signaling pathway	Antioxidant and anti-inflammatory properties	[77]
8.	Gossypol	Polyphenolic Aldehyde	***Gossypium***	Malvaceae	Whole plant	It prohibits production and motility of male gametes It acts as an antifertility agent by thwarting enzymes that are involved in energy providing metabolic reactions (in sperm producing cells and spermatozoa)	Antifertility, antivirus, anticancer, antioxidant, antitrypanosomal, antimicrobial, and antimalarial activities	[44]
9.	Linalool	Acyclic Monoterpenoid	***Hyptis crenata***	Lamiaceae	Leaves	Inhibit the activity of the respiratory chain dehydrogenase enzyme.	Antiproliferative antioxidant and cytotoxic and effects, antibacterial and insecticidal activity, ulcer healing properties.	[45]
10.	Lycopene	Carotenoid	***Solanum lycopersicum***	Solanaceae	Fruit	Lycopene is a powerful quencher of singlet oxygen which is an active form of oxygen, signifying its role as a more effective antioxidant.	Antioxidant activity	[46]
11.	Piperine	Alkaloid	***Piper nigrum***	Piperaceae	Fruit	Inhibit the activity of EGFR tyrosine kinase enzyme.	Reduction of insulin-resistance, anti-inflammatory effects	[46]
12.	Platycodon saponin	Amphipathic Glycosides	***Platycodon grandiflorum***	Campanulaceae	Roots	Functional inhibition of NF-κB and PI3K / AKT and MAPK signaling pathways.	Anti-cancer cytotoxic cells, Antiviral activity neuroprotective activity, Cholesterol lowering properties	[78]
13.	Quercetin	Polyphenolic Flavonoid	***Capparis spinosa***	Capparaceae	Leaves	Blockage of the PI3K / AKT pathway leading to a reduction in the expression of anti-apoptotic protein Bcl-w.	Antioxidant and hepatoprotective effects, Anti-cancer	[47]
14.	Resveratrol	Polyphenols	***Vitis vinifera Linnaeus*** (grapes)	Vitaceae	Fruit	cell survival signals inhibitor, p53 activation Apoptosis Inhibitor	Anti-cancer Anti-oxidant Anti-inflammation Cardioprotection	[48]
15.	Sesquiterpene Coumarins	Terpene	***Mikania spp***	Asteraceae	Leaves and aerial parts	Restrain the exflagellation of Plasmodial male microgamete by causing DNA damage in cells undergoing replication.	Cytotoxic activity Antibacterial activity anti-inflammatory and antitumor activity.	[49]

(*continued on next page*)

Table 2 (*continued*)

	Bioactive compound/ Natural product	Category/ Chemical nature	Origin/source plant	Plant family	Plant part used	Mechanism of action	Biomedical application	References
16.	Sesquiterpenoids	Terpene	***Inula linearifolia***	Asteraceae	Aerial parts	Act in response to the active groups accessible in proteins and enzymes, particularly the thiol group.	Induction of apoptosis, Cytotoxic activity; Inhibition of breast cancer cell growth	[50]
17.	Ursolic acid	Triterpenoids	***Ocimum basilicum***	Lamiaceae	Whole plant	significant action in glucose homeostasis, reduces diabetic blood glucose levels, Improves the glucose and insulin tolerance, surges insulin synthesis and release from pancreas and prevents protein glycation	Antiviral activity Antiproliferative activity	[51]
18.	Withaferin A	Withanolide	***Withania somnifera***	Solanaceae	Leaves	Drug interacts with C-terminus of Hsp90, thus provoking degradation of heat shock proteins.	Antioxidant activity, Anti-proliferative	[52]
19.	Apomorphine	Dopamine receptor agonist	***Papaver somniferum***	Papaveraceae	Unripe capsules	Drug acts by enhancing motor function and vasodilation by exciting dopamine receptors (D2) in hypothalamus, pituitary gland, and blood vessels.	Parkinson's disease	[53]
20.	Arteether	Sesquiterpene trioxane lactone	***Artemisia annua***	Asteraceae	Leaves	Inhibit the nutrient flow to erythrocytic stage of parasite (*P. falciparum*) by modifying properties of membranes.	Antimalarial	[54]
21.	Galantamine	Amaryllidaceae alkaloid	***Galanthus woronowii***	Amaryllidaceae	Bulb	Esclates acetylcholine neurotransmission	Alzheimer	[55]
22.	Nitisinone	Mesotrione	***Callistemon citrinus***	Myrtaceae	Roots	It causes obstruction in the catabolic pathway of tyrosine that leads to a decline in the accumulation of venomous metabolites in HT-1.	Hepatorenal tyrosinemia Anti-cancer activity	[56]
23.	Paclitaxel	Taxane diterpene	***Taxus brevifolia Nutt.***	Taxaceae	Bark	Alleviates microtubules and diminish their dynamicity. Endorse arrest of mitosis and cell death.	Anti-cancer activity	[57]
24.	Tiotropium	Muscarinic receptor antagonist	***Atropa belladonna***	Solanaceae	leaves and roots	Acts on specific muscarinic receptors located in the respiratory tract to cause relaxation of smooth muscles and dilation of bronchioles.	Asthma and COPD (*Chronic obstructive pulmonary disease)*	[58]

Abbreviations: COX-2, cyclooxygenase-2; COPD, chronic obstructive pulmonary disease; HT-1, Hepatorenal tyrosinemia-1; dopamine receptors (D2); Hsp90, heat shock protein 90; PI3K, Phosphoinositide 3-kinase; PKB, protein kinase B; MAPK, mitogen-activated protein kinase; NF-κB, Nuclear factor kappa B; IL-8, Interleukin 8; IL-6, Interleukin 6; TNFα, tumor necrosis factor-alpha; AMPK, AMP-activated protein kinase; EGFR, epidermal growth factor receptor.

compounds have been known as the widely abundant and efficient source of new anti-cancer drugs [62].

Various scientific evidences signify the importance of a number of phyto-chemicals in cancer therapeutics [63]. Phyto-chemicals which have been established carrying anti-cancer activity through have a number of consistent mechanisms for slowing down the cancer progression by declining survival and proliferation of malignant cells, removing free radicals, and reducing the angiogenesis of tumors [64]. They work with a wide range of complex mechanisms of action in many signaling pathways including membrane receptors, oncoproteins or tumour-suppressor proteins, transcription factors, microRNAs and caspases [65]. A few therapeutic bioactive compounds have been identified (Table 4) that has shown therapeutic potential in the management of OMCs. For instance Epicatechingallate derived from leaves of *Camelia sinesis*, Gingerol isolated from *Zingiber officinale* roots and Benzylisothiocyanate extracted from seeds of *Moringa oleifera* has been tested for their efficacy against oral cancer [66–68].

Epicatechingallate mediates anti cancerous activities such as inhibition of migration, invasion, angiogenesis, and promotion of apoptosis through modulating the production of reactive oxygen species (ROS), inhibiting the pathway associated with nuclear factor-κB signaling, promoting the modifications at epigenetic level through regulating acetylation of histones and inhibiting DNA methyltransferase activity [69]. Gingerol mediates anti cancerous activity in oral cancer by inducing apoptosis and arresting cell cycle [70]. Oral cancer when treated with Benzylisothiocyanate there is a rapid production in reactive oxygen species that promote DNA damage, which along with redox stress activates p21 and p53, resulting in cell cycle arrest [71]. Resveratrol, solasonine, curcumin and several other bioactive compounds are found to be effective against skin cancer.There is a paucity of the use of plant bioactive compound and libraries in the management of OMCs. Hence, there is a pressing need to employ both in-silico and in-vitro approaches to develop compound libraries that would be amenable for the identification of useful therapeutic targets for OMC cancers in the era of precision medicine.

6. Conclusion and future perspectives

Cancer, a foremost public health issue, has a profound influence across the globe and influencing both developed as well developing countries [72]. Given the severity of cancer, its handling and treatment has been an enduring struggle with insignificant accomplishment. Presently available cancer treatment includes surgical removal following radiation treatment for a cancer mass, which is often followed

Table 3
List of commercially accessible plant derived compounds/drugs for treating numerous cancers.

	Cancer type	Plant Family	Plant	Plant Part Used	Phyto Compound	Type of studies	References
1.	Bladder Cancer	Theaceae	*Camellia sinensis*	Leaves	Epicatechingallate	Both in vitro and in vivo	[79]
		Zingiberaceae	*Zingiber officinale*	Roots	Gingerol	Both in vitro and in vivo	[80]
		Plumbaginaceae	*Plumbago zeylanica*	Roots	Plumbagin	In vitro	[81]
2.	Blood Cancer	Ranunculaceae	*Clematis manshrica*	Flower and Leaves	Benzoquinone	In vivo	[82]
		Plumbaginaceae	Plumbago zeylanica	Roots	Plumbagin	In vitro	[83]
		Theaceae	*Camellia sinensis*	Leaves	Epigallocatechin gallate	In vivo	[84]
		Zingiberaceae	*Curcuma longa*	Rhizome	curcumin	In vitro	[85]
3.	Brain Cancer	Vitaceae	*Vitis vinifera*	Leaves	Resveratol	Both in vitro and in vivo	[86]
		Theaceae	Camellia sinensis	Leaves	Epigallocatechin gallate		[87]
4.	Breast Cancer	Cannabinaceae	*Cannabis sativa*	Leaves	Cannabinoid	Both in vitro and in vivo	[88]
		Rhamnaceae	*Ziziphus spina-christi*	Flowers and Leaves	Doxorubicin	In vivo	[89]
		Apiaceae	*Centella asiatica*	Leaves	Asiatic acid	In vitro	[90]
		Theaceae	*Camelia sinesis*	Leaves	Epicatechingallate, picatechin, epigallocatechin	Both in vitro and in vivo	[91]
		Araliaceae	*Panax ginseng*	Leaves	Panaxadiol	Both in vitro and in vivo	[92]
		Zingiberaceae	*Zingiber officinale*	Roots	Gingerol	In vitro	[93]
		Zygophyllaceae	*Peganum harmala*	Roots	Harmine	In vitro	[94]
		Apiaceae	*Centella asiatica*	Whole plant	Tamoxifen	Both in vitro and in vivo	[95]
		Rhamnaceae	*Ziziphus jujuba*	Fruits, Seeds and Leaves	Linoleic acid	In vivo	[96]
		Lamiaceae	*Ocimum sanctum*	Leaves	Eugenol	Both in vitro and in vivo	[97]
		Cucurbitaceae	*Momordica charantia*	Leaves and Roots	Charantin	In vitro	[98]
5.	Cervical Cancer	Amaryllidaceae	*Allium sativum*	Buds and Leaves	Allicin	In vivo	[99]
		Rhamnaceae	*Ziziphus mauritiana*	Leaves, Bark and Fruits	Methyl stearate	In vitro	[100]
		Crassulaceae	*Bryophyllum pinnatum*	Leaves	Bryophyllin	In vitro	[101]
		Solanaceae	*Withania somnifera*	Roots, Stem and Leaves	5-Fluorouracil	In vitro	[102]
		Zingiberaceae	*Zingiber officinale*	Roots	Gingerol	In vitro as well as In vivo	[103]
6.	Colon Cancer	Araliaceae	*Panax ginseng*	Leaves	Panaxadiol	In vitro	[104]
		Ginkgoaceae	*Ginkgo biloba*	Leaves	Bilobalide	In vitro	[105]
		Vitaceae	*Vitis vinifera*	Seeds extract and Fruits	Procyanidins	In vivo	[106]
		Zingiberaceae	*Curcuma longa*	Rhizomes	Curcumin, ascorbic acid	Both in vitro and in vivo	[107]
		Moringaceae	*Moringa oleifera*	Seeds	benzylisothiocyanate,4-benzylisothiocyanate	In vitro	[108]
		Passifloraceae	*Passiflora caerulea*	Flowers	Chrysin	In vitro	[109]
		Solanaceae	*Capsicum annuum*	Pepper	Luteolin	In vitro	[110]
		Dioscoreales	*Dioscorea colletti*	Rhizomes	Dioscin	In vitro	[111]
7.	Gastric Cancer	Schizophyllaceae	*Schizophyllum commune*	Fruiting bodies	Quecertin	Both in vitro and in vivo	[112]
8.	Head and Neck Cancer	Betulaceae	*Betula* Sp.	Leaves	Betulinic acid	In vitro	[113]
		Zingiberaceae	*Curcuma longa*	Rhizomes	Curcumin	Both in vitro and in vivo	[114]
		Rhamnaceae	*Ziziphus spina-christi*	Flowers and Leaves	Doxorubicin	Both in vitro and in vivo	[115]
9.	Leukemia	Asteraceae	*Xanthium strumarium*	Fruits	Xanthatin	In vitro	[116]
		Zingiberaceae	*Curcuma longa*	Rhizomes	Curcumin, ascorbic acid	In vitro	[117]
		Polygonaceae	*Fagopyrum sculentum*	Seeds	Buckwheat inhibitor-1protein	In vitro	[118]
		Convolvulaceae	*Ipomoea batata*	Roots	Trypsin inhibitor protein Promyelocytic	In vitro	[119]
		Asteraceae	*Xanthium strumarium*	Fruit s	Xanthatin	In vitro	[120]
10.	Liver Cancer	Dioscoreales	*Dioscorea colletti*	Rhizomes	Dioscin	In vitro	[121]
		Malvaceae	*Hibiscus mutabilis*	Pepper	Lectin	In vitro	[122]
		Polygonaceae	*Polygonum cuspidatum*	Whole plant	Resveratrol	In vitro	[123]
		Lamiaceae	*Ocimum sanctum*	Leaves	Eugenol, orientin, vicenin	Both in vitro and in vivo	[124]
		Solanaceae	*Solanum nigrum*	Leaves	Solasonine	In vitro	[125]
		Asclepiadaceae	*Asclepias curassavica*	Aerial parts	Cardenolides	In vitro	[126]

(*continued on next page*)

Table 3 (*continued*)

	Cancer type	Plant Family	Plant	Plant Part Used	Phyto Compound	Type of studies	References
		Nelumbonaceae	*Nelumbo nucifera*	Embryos	Neferine	In vitro	[127]
		Theaceae	*Camelia sinesis*	Leaves	Epicatechingallate	In vitro	[128]
		Moringaceae	*Moringa oleifera*	Seeds	Benzylisothiocyanate	In vitro	[129]
		Rhamnaceae	*Ziziphus spina-christi*	Flowers and Leaves	Doxorubicin	In vivo	[130]
		Iridaceae	*Saffron crocus*	Dry stigmas	Saffron	Bothin vitro and in vivo	[131]
		Solanaceae	*Solanum nigrum*	Leaves	Solasonine	In vitro	[132]
		Theaceae	*Camellia sinensis*	Leaves	Theabrownin	In vivo	[133]
		Liliaceae	*Crocus sativus*	Dry stigmas	Crocetin	In vivo	[134]
		Podophyllaceae	*Podophyllum peltatum*	Leaves	Podophyllotoxin	In vitro	[135]
11.	Lymphoma	Rhamnaceae	*Ziziphus rugosa*	Pericarp and Seeds	Betulinic acid	In vivo	[136]
12.	Nasopharyngeal Carcinoma	Fabaceae	*Phaseolus vulgaris*	Seeds	Lectin	In vitro	[137]
		Zingiberaceae	*Curcuma longa*	Rhizomes	Curcumin	In vitro	[138]
13.	Ovarian Cancer	Annonaceae	*Annona squamosa*	Seeds	Bullatacin	In vitro	[139]
		Zingiberaceae	*Zingiber officinale*	Rhizomes	6-Shogaol	In vitro	[140]
		Amaryllidaceae	*Allium sativum*	Buds and Leaves	Allicin	In vitro	[141]
14.	Pancreatic Cancer	Amaryllidaceae	*Allium sativum*	Buds and Leaves	Allicin	In vitro	[142]
		Zingiberaceae	*Zingiber officinale*	Roots	Gingerol	Both in vitro and in vivo	[143]
		Theaceae	*Camelia sinesis*	Leaves	Epicatechingallate	Both in vitro and in vivo	[144]
15.	Prostate Cancer	Cannabinaceae	*Cannabis sativa*	Leaves	Cannabinoid	Both in vitro and in vivo	[145]
		Theaceae	*Camellia sinensis*	Leaves	Epigallocatechin gallate	In vivo	[146]
		Solanaceae	*Solanum lycopersicum*	Fruits	Lycopene	In vivo	[147]
		Fabaceae	*Cicer arietinum*	Seeds	Bowman-Birk-type protease	In vitro	[148]
		Polygonaceae	*Polygonum cuspidatum*	Whole plant	Resveratrol	In vivo	[149]
16.	Stomach Cancer	Asphodelaceae	*Aloe barbadensis*	Leaves	Emodin	In vivo	[150]

Table 4
List of commercially available plant derived compounds/drugs for treating oral mucocutaneous cancers (OMCs) and Skin Cancers.

	Cancer type	Plant Family	Plant	Plant Part Used	Phyto Compound	Type of studies	References
1.	Oral Cancer	Theaceae	*Camelia sinesis*	Leaves	Epicatechingallate, picatechin, epigallocatechin	Both in vitro and in vivo	[66]
		Zingiberaceae	*Zingiber officinale*	Roots	Gingerol	In vitro	[67]
		Moringaceae	*Moringa oleifera*	Seeds	Benzylisothiocyanate	In vitro	[68]
2.	Skin Cancer	Polygonaceae	*Polygonum cuspidatum*	Whole plant	Resveratrol	In vitro	[151]
		Apocynaceae	*Carissa spinarum*	Fruits	Alkaloids, saponins, tannins, flavonoids	In vitro	[152]
		Solanaceae	*Solanum nigrum*	Leaves	Solasonine	In vitro	[153]
		Plumbaginaceae	*Plumbago zeylanica*	Roots	Plumbagin	In vitro	[154]
		Zingiberaceae	*Curcuma longa*	Rhizomes	Curcumin	In vitro	[155]

by treatment with the use of preservative chemicals [73]. Existing chemotherapeutic treatments include DNA-interactive compounds like Cisplatin, antimetabolites (e.g. Methotrexate), hormones, anti-tubulins including taxanes, in addition to cell identification agents [74]. The main disadvantage of chemotherapy is the cancer relapse, drug resistance, along with lethal effects on unintended tissues obstructing the usage of anti-cancer drugs, consequently affecting the patient's survival and life quality [75]. To overcome current medical problems, we must look for novel and effective anticancer agents carrying improved efficacy and minimum side effects. We have discussed in this review the potential for the use of bioactive plant compounds as potential complementary approach to the management of OMCs which have high burdens in India and Africa. We have also highlighted the benefit of the use of high throughput omics technique to develop medicinal and anti-OMC cancerous compound libraries from widely endemic plants in these regions. Furthermore, a catalog of bioactive compounds libraries used for various cancers, including OMCs has been provided. It is hoped that bioactive compounds would be further explored for the management of oral and maxillofacial diseases, particularly, OMCs.

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Conflict of interest statement

The authors declare that they have no competing interests.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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