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Review

Treatment failure shortcomings, possible causes and upcoming phyto-optimism in oral cancer

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Abstract: Oral cancer (mainly oral squamous cell carcinoma or OSCC) is a dangerous health problem and the sixth foremost cancer globally. Current oral cancer treatments include surgery, chemoradiation therapy, targeted therapy, and immunotherapy. Despite recent progress, resistance to classical chemotherapeutic drugs, radiation therapy, targeted chemo-drug/monoclonal antibodies, and even the resistance to Immuno-Checkpoint Inhibitors remains hurdle for OSCC treatment and cause disease relapses. Many therapeutic agents induce drug resistance (DR), which varies among oral cancer patients. The DR can be intrinsic or acquired; knowing the DR mechanisms is essential. The constantly evolving OSCC cells with effective energy management, though, get adapted to drug pressure but respond to many plant-based extracts and purified phytochemicals. Though DR appears to be a never-ending process, improvising plant-based phytochemical/s with different cocktail formulations, nano-based modifications, or modern technology has tremendous potential. A better understanding of DR and chemoprevention can show the path to future personalized therapy approaches.

Keywords: oral cancer; treatment failure mechanisms; therapy-resistance; phytochemical/s

1. Introduction

Oral cancer is the leading cause of cancer-related death in south-east Asia and India [1]. OSCC (oral squamous cell carcinoma) is the most common among different types of mouth cancers. Advancement of research in this field comes with numerous drugs and therapeutic strategies, and many of these work well in the primary/initial stages of treatment. Current primary therapies for oral cancer include surgery, chemo/radiation therapy, targeted therapy with small molecular inhibitors (SMI), and monoclonal antibodies or immunotherapy (MAbs) [2, 3]. Despite intense research and successes in treating oral cancers, cisplatin is the primary chemotherapeutic drug to treat OSCC.

Conversely, numerous oncogenes and signaling molecules supported OSCC survival over the years and found lucrative targets [4]. Chemotherapeutic anti-cancer agents like cisplatin form DNA adducts, and 5BU (5-Bromouracil) gets incorporated with rapidly growing tumor cells, causing DNA damage, reducing proliferation, and promoting cell death. However, most of these chemo drugs have an off-target effect on healthy normal cells causing high toxicity and side effects [5]. Therapeutic resistance for nontargeted chemo-drugs, for radiation treatment, targeted (SMIs) chemo-inhibitors/TKIs (erlotinib, gefitinib, and lapatinib), and monoclonal antibodies (cetuximab, panitumumab against EGFR) and Immune Checkpoint Inhibitors (nivolumab against PD1) have been reported.

These drugs are effective during early treatment, but patients develop recurrent cancer as treatment of oral cancer proceeds [6]. Later, most of these tumor cells adapt to pharmaceutical treatment and become DR. Drug resistance leads to most cancer-related deaths [7, 8]. Besides the chemotherapeutic drugs, resistance to immune checkpoint inhibitors (ICI) has also been reported for OSCC. These DR mechanisms vary significantly among different patients, tumor stage/grade, cancer cell types, and nature/dose of the drug [9]. Hence, DR can be varied from patient to patient and is difficult to classify. The cancer cells offer intrinsic/inherent or acquired resistance. The intrinsic resistance is inbuilt with the patient and present before drug treatment; on the other hand, the acquired resistance is induced by the cancer cells after therapy.

Intrinsic/innate resistance to particular drug/s has been observed in many oral cancer patients. These patients do not respond to drugs because of pre-existing factors. These factors include specific genetic mutations, deletions, amplifications, alternative splicing, or post-translational protein modifications. A minor subpopulation of treatment-

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selected cells behaves like cancer stem cells (CSCs) and causes tumor relapse [6, 10]. Upon cisplatin treatment, many oral tumor cells showed PI3K-Akt, EGFR-MAPK, JAK-Stat3, CD44, and Nanog overexpression [11-15]. The high activation of EGFR, PI3K, and Akt pathways activate TFs (transcription factors) like AP-1, NFκB, p53, Snail, Slug, etc., causing EMT (epithelial-mesenchymal transition) of OSCC [16, 17]. Other defensive CSC strategies, like increased drug efflux (mediated by ABC transporter), and detoxifying drug (via glutathione S-transferase system), have been reported in OSCC. Similarly, the overexpression of CD44, ALDH1A1/3A1, and Nanog in a minor population of OSCC cells promotes cisplatin-resistant [11, 12, 17]. Similarly, the minor subpopulation with more self-renewal programs and survival makes it more therapy-resistant [10, 13-15]. Intrinsic therapy resistance is a vital problem in OSCC.

In acquired resistance, the efficacy of an anti-cancer drug gradually decreases after the drug treatment. In the acquired resistance, the drug target gets modified or mutated over time [10, 18, 19]. The DNA repair ability of OSCC cells affects the therapeutic efficacy of platinum compounds and poly ADP-ribose polymerase inhibitors. It causes acquired resistance in OSCC [20]. The shifting of EGFR mutations caused therapy resistance to first, second, and third-generation TKIs (tyrosine kinase inhibitors) in cancer [21-24], including OSCC. Likewise, the imatinib (TKI) induced mutations of BCR-ABL kinase within the target kinase domain have been reported that cause acquired resistance in cancer [25]. Resistance to immune therapy caused due to the acquired defect of tumor-specific antigen expression (PD1, PD-L1, or CTLA4) in OSCC [26]. Hence acquired resistance is also widely observed in OSCC [27].

Other mediators can cause innate or acquired resistance in OSCC. These include the activation of proto-oncogene/s, miRNA, lncRNA, circ-RNA, mutations, drug target alterations, tumor microenvironment (TME) changes, and mobilization of these molecules through micro-vesicles or exosomes after treatment. With all these molecular players of diverse characters, the story of the DR in OSCC is lengthy and complicated. These scenarios warrant a refined understanding of the DR mechanism in OSCC for better therapeutics.

2. Drug resistance mechanism in OSCC

Oral cancer patients are treated with chemotherapy (including nontargeted cisplatin, carboplatin, docetaxel, paclitaxel, adriamycin, doxorubicin, epirubicin, pirarubicin, methotrexate and 5-FU, i.e., 5-fluorouracil or targeted SMI like erlotinib, sunitinib, sorafenib, olaparib, etc.) or radiotherapy (2D, 3D-CRT and IMRT) or both types. The patients also receive immunotherapy (targeted immunotherapy, i.e., cetuximab, bevacizumab,

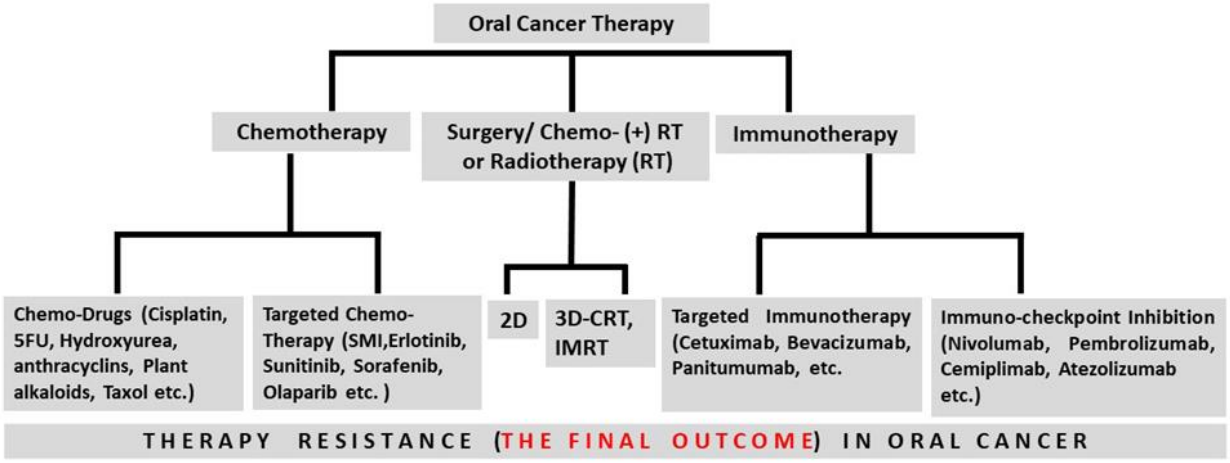

Figure 1: Common treatment strategy for oral cancer: Oral cancer is mainly treated by surgery; surgery and radiation; surgery, positive loco-regional lymph node removal (LRLNR) and radiation; surgery, LRLNR, radiation and chemotherapy; or palliative care with only radiotherapy based on tumor site, type of tumor, stage/ grade and biopsy status of nearby lymph nodes. The therapy resistance is mainly seen in the treatment of all three major classes: (A) Chemotherapy, (B) Radiation therapy and (C) Immunotherapy. (A) It's not a remedial modality alone; it's administered before surgery (induction) and/or with irradiation/ post-surgery chemoradiotherapy. The common use of adjuvant chemoradiotherapy has been seen. The chemotherapy drugs (cisplatin, 5-FU, methotrexate, hydroxyurea, anthracyclines, platinum derivatives, alkaloids, and toxoids) and targeted chemo-drugs against RTKs (erlotinib, gefitinib, sorafenib, sunitinib etc.), and drugs that block GF receptors/ enzymes (sirolimus) were used. (B) Radiotherapy (RT) is used only if the tumor is inoperable as a palliative choice for terminal cases and combined with chemo/ targeted therapy. The 3D-CRT (3-dimensional conformal RT) and intensity-modulated RT (IMRT) are used to protect (e.g., optic nerve, brainstem, spinal cord and parotid glands) vital organs. (C) The targeted immunotherapy drugs, including monoclonal antibodies (cetuximab, panitumumab, bevacizumab, etc.), ICIs (nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab etc.) have been used. Many of these strategies work fine during the initial days but lead to DR.

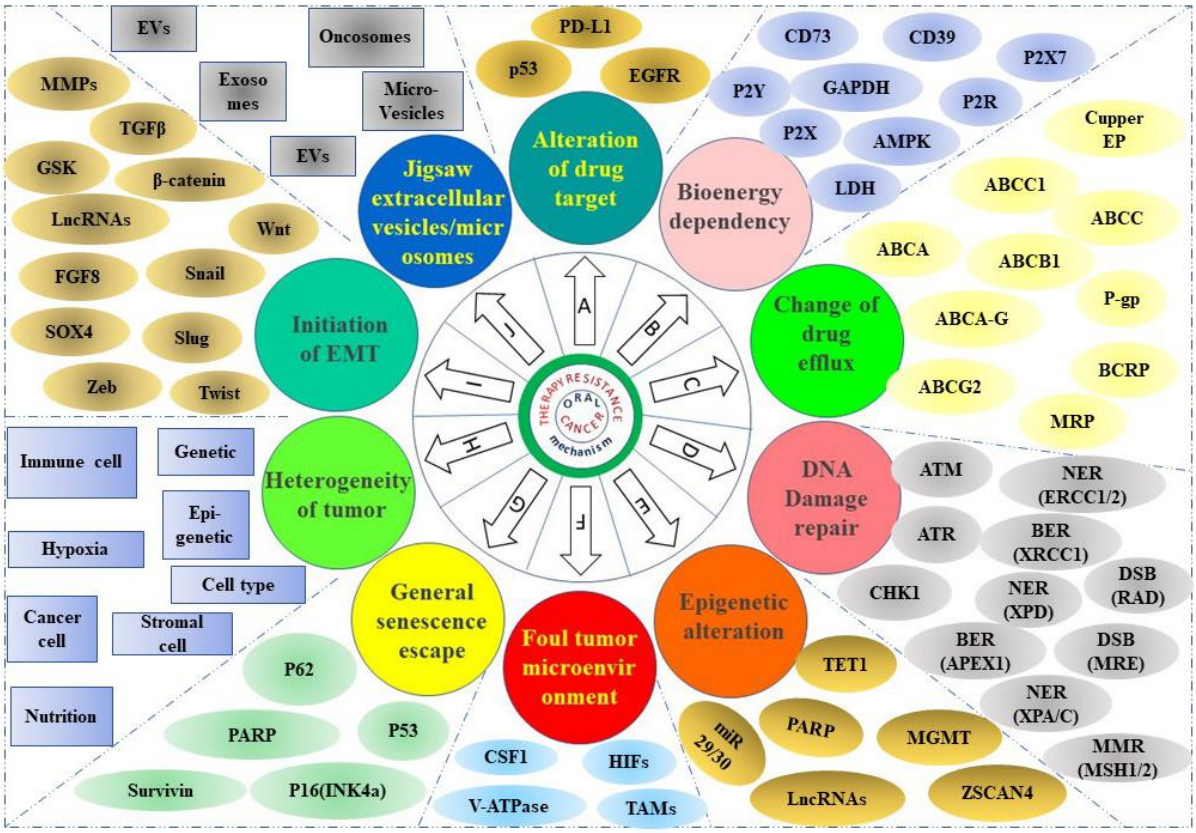

Figure 2: Mechanism of treatment failure in OSCC. Treatment failure is the primary concern and raises the question of using single-molecule/ single targets on cancer. Here the common treatment failure mechanisms (A-J) have been projected (A) Alteration of Drug Target; (B) Bioenergy dependency; (C) Change of drug efflux; (D) DNA Damage Repair; (E) Epigenetic alteration; (F) Foul tumor microenvironment (G) General senescence escape; (H) Heterogeneity of tumor; (I) Initiation of EMT; and (J) Jigsaw Extracellular Vesicles/microsomes as discussed in the text.

panitumumab, etc., and immuno-checkpoint inhibition with nivolumab, pembrolizumab, cemiplimab, atezolizumab, etc.) [8, 28-31] for their treatment as depicted in figure 1.

However, the OSCC is challenging to treat by using these drugs. So, at the end of each treatment, there is only one outcome, i.e., drug resistance. Each oral tumor's DR pattern appears different [29, 32]. This can depend on several genetic, epigenetic, and other factors [33]. There is a great variation of DR on a patient-to-patients basis [9] which is vital for treatment success [34]. Here, the oral cancer DR mechanisms are summarized under these subheadings: alteration of drug target, bioenergy dependency, change of drug efflux, DNA damage repair, epigenetic alteration, foul tumor microenvironment, and general senescence escape, heterogeneity of tumor and initiation of EMT. Many of these factors move through the extracellular vesicles and make the sensitive oral cancer cells resistant have also been discussed (figure 2).

2.1 Altering drug target

Alteration of drug targets (ADT) is where the drug target molecule gets altered with drug selection pressure. ADT is evident in DR or recurrent oral tumor patients. OSCC is treated with many targeted therapies, which in many cases leads to therapeutic resistance [35-37]. Prolonged exposure of OSCC cells to the drugs like afatinib, MK2206, BEZ235, olaparib, and cisplatin caused a nearly eight-fold rise in the mutational rate [38]. This reduced several advantages of targeted therapy over traditional chemotherapies, which are often toxic to normal cells. The ADTs occur due to the generation of a secondary mutation/s or epigenetic modifications [36, 37] affecting the drug target.

Wild-type (wt) p53 senses cellular DNA damage and activates the responses [39]. P53 mutation at the DNA binding domain can predict the therapy resistance in OSCC [40]. Upon selection pressure, the cancer cell with wt-p53 acquired p53 mutations [36, 37], which fails the DNA repair [36], and offers treatment resistance [35]. Many EGFR inhibitors are initially effective and subsequently cause drug-induced mutations in OSCC [41-43]. The EGFR T790M mutations were described among OSCC patients [44], which endorses acquired resistance [22]. Similarly, the resistance to ICI therapy in OSCC [45] could be due to the loss of antigen presentation, and epigenetic modification/s. The lack of memory T-cells, defects of interferon pathways, and upregulation of other immune checkpoints [46] could be other mechanisms. These drugs induced mutations caused in therapy resistance of OSCC.

2.2 BioEnergy dependency

All living cells, including cancer cells, need energy for their survival. ATP, either in the extracellular tumor microenvironment, supports metabolism and even therapeutic resistance [47]. The inhibitors of GAPDH and LDH (like 3-bromopyruvate or oxamate and FX11) reduce ATP (intracellular) levels and sensitize them to therapy. Cetuximab inhibits glucose uptake and lactate production and reduces cellular ATP levels of OSCC [48]. The OSCC cells with elevated AMPK activity were less sensitive to cetuximab-induced growth inhibition [49]. The increased intracellular ATP competes with the inhibitors of RTK (receptor TKs)/TK (tyrosine kinases) or enhances drug (ABC transporters) efflux, causing therapy resistance. The purinergic receptors help import ATP [50] and support the carcinogenesis and chemoresistance of cancer [51]. Purinergic receptors (P2X/Y, P2R) are involved in the therapy resistance of OSCC [11, 14, 15, 52]. This purinergic receptor-mediated signaling activates interleukins and TFs (c-Jun/NFκB) in OSCC [53, 54]. Extracellular ATP activates and increases glucose transporter-1 in cancer cells via P2X7 [55], causing therapy resistance in OSCC [11-14]. ATP released from stressed cells degrade to AMP/ adenosine by CD39/73 and is observed in OSCC [56] linked with resistance. Adenosine signaling affects extracellular ATP and promotes immunosuppression and therapy resistance in OSCC [57, 58].

2.3 Change of drug efflux (DE)

The efflux of anti-cancer drugs plays a vital role in chemotherapy resistance. The intrinsic or acquired causes can promote this ATP-driven DE [8]. The human genome has 48 ABC transmembrane transporter DE genes that belong to seven subfamilies (ABCA to G) [59]. The expression of ABCB1/C1/G2 was found to be linked with the DE of many drugs (anthracyclines, bisantrene, camptothecins, epipodophyllotoxin, flavopiridol, mitoxantrone, and TKIs-gefitinib/imatinib). These ABCA-G molecules removed cisplatin, doxorubicin, etoposide, paclitaxel, and vinblastine and were elevated in chemotherapy-treated OSCC patients [60-62]. The overexpression of ABC-B1/C1/G2 was involved with the therapy resistance of OSCC [60, 63, 64]. ABCB1/C1/G2 upregulation was found in cisplatin-resistant OSCC [34, 65, 66]. Similarly, the patients with more MDR(P-gp), MRP, and BCRP were associated with therapy resistance [34]. All these drug efflux molecules cause therapy-resistant in OSCC [66, 67]. Different signaling pathways like Hh (5-FU and cisplatin-resistant OSCC)/ABC transporters [60], Nrf2-induced expression of ABCG2 in CSCs [68], Notch1 driven ABC transporters [69], MAPK (JNK) propelled MDR (p gp) [70] and p38 MAPK induced Hsp27/ABCG2/MDR-1 causing therapy resistance in OSCC [63]. All these signaling pathways fuel many gene upregulations causing therapy failure, DR, and tumor relapse in OSCC.

2.4 DNA damage repair

DNA damage is induced by many chemotherapy drugs that kill cancer cells. The higher DNA damage response (DDR) to the anti-cancer drugs can reduce the drug efficacy (by DNA lesion repairs), leading to resistant OSCC [71, 72]. The DDR also affects DNA repair, cell cycle, cell death control, and senescence. The DNA damage induced by chemotherapy and ionizing radiation activates/ stabilizes the p53 pathway/protein. Different protein kinase sensors like ATM/ATR and other (effector) kinases, such as Chk1/2 and Wee1, participate in therapy resistance in OSCC [73]. Mutation/inactivation of the p53 offers therapy resistance in OSCC [74]. The increased expression/activity of nucleotide excision repair (NER) genes (ERCC1/2, XPA/C/D), base excision repair (BER) genes (like APEX1, XRCC1), the (DSB) double-strand breaks repair genes (MRE11A, RAD50/51, XRCC2), and (MMR) mismatch repair genes (MLH1, MSH2/3) were associated with OSCC resistance [20, 75-77]. The proteins that guard DNA replications/ repair (BRCA1/2, LIG1, DNA2, POLD1, MCM2, and RAD54B) offer DNA stability (ATR/CHK1), homologous recombination (Rad51, CDK1/Chk1), and DNA safeguarding (PARP), causing therapy resistance OSCC [38, 78-80].

2.5 Epigenetic alterations

Epigenetic alterations play a role in eukaryotic gene regulation and therapy resistance in OSCC. Epigenetic changes like the remodeling of chromatin, histone modifications, DNA methylations, and non-coding RNA alterations contribute to the regulation of CSC features, drug efflux, DNA repair, apoptosis failure, and treatment resistance in OSCC [81]. Induced DNA methylation has been observed in therapy-resistant OSCC, HNSCC specimens, and cells [82]. The radiation (OSCC) resistant rSCC-61 cells showed increased DNA methylation over the radiation-sensitive counterpart [83]. Conversely, ten-eleven translocation 1 (TET1) regulates o6-methylguanine-DNA methyltransferase (MGMT) in chemotherapy resistance OSCC [84]. DNA methylation of DPD (dihydro pyrimidine dehydrogenase) has been reported in the 5-FU resistance of OSCC [85]. ALDH1 (Aldehyde dehydrogenase-1) and PD-L1 promote therapy resistance in OSCC, and the treatment of DNA hypomethylating agents reverses this condition [86].

Recently, histone acetylation [87], epigenetic alterations [82], chromatin remodeling [82], and the non-coding RNAs (lncRNAs) participate in epigenetic alterations and resistance to therapy in OSCC [82]. Targeting epigenetic pathways reduced ZSCAN4 (Zinc finger and SCAN domain containing 4) and reduced stemness/ therapy resistance [88]. Several microRNAs (miRNAs) play a role in the DR of OSCC [89, 90]. Many miRNAs were identified in developing cisplatin resistance in OSCC [65]. The miR-30a promotes 5-FU-resistant [91], miR-29a-3p enhances radioresistance [92], miR-224-5p promotes docetaxel

resistance [93], and miR-155/ miR-619-5p/ miR-30a promotes cisplatin resistance [94-96], and miR-371/-372/-373/-1246 enhances the therapy resistance [97-99] of OSCC. The lncRNAs like LHFPL3-AS1 and lncRNA PVT1 were involved in oral cancer development and cisplatin resistance [89, 100, 101]. Further, lncp23154 [101], lncRNA (HOXA11-AS), and lncRNA ANRIL also regulate the cisplatin resistance of OSCC [102, 103]. All this evidence suggests that both miRNA and lncRNA contribute to the therapy resistance of oral cancer.

2.6 Foul tumor microenvironment

Tumors contain different types of cells and extracellular (ECM) matrix. The TME includes physical, chemical (the acidic/ hypoxic environment), and biological environment (ECM components, fibroblast, blood cells/ vessels, immune and inflammatory cells, nutrients/ GFs, and signaling molecules) to resist anti-cancer treatment. The acidic (pH 6.5-7.1) extracellular TME contributes ('ion trapping' of weak base anti-cancer drugs at extracellular TME), causing the therapy resistance. Therapeutic approaches to reducing acidic TME with PPIs (proton pump inhibitors) overcome treatment resistance [104, 105], including OSCC [106, 107]. The inhibition of V-ATPase was effective against multidrug resistance in OSCC [108-110), esophageal carcinoma [111], and oral epidermoid carcinoma [112, 113].

A hypoxic TME triggers hypoxia-inducible factors (HIFs) that promote chemoradiation resistance in OSCC [114]. Post-treatment changes in TME contribute to the success of chemotherapy in OSCC, and TAM (tumor-associated macrophase)-targeted therapy [115-117]. Targeting toll-like receptor-3 in OSCC decreased TAM and sensitized cisplatin resistance, causing tumor regression [118, 119]. Over secretion of CSF1 (colony-stimulating factor-1) by macrophages promotes aggressiveness [120-123], while blocking CSF1 overcomes OSCC therapy resistance [124]. Many other growth factors induce EGFR-TKIs resistance in OSCC [125-128].

TME heterogeneity also contributes to therapy resistance. The variations of TME vasculature inside tumors change the hypoxia level. This leads to fluctuations in O2 levels causing oxidative stress-mediated DNA damage, genetic instability, clonal subpopulations, and back therapy resistance. TAMs of the TME release miRNA-containing exosomes, which add to OSCC DR [129]. The other TME molecules include H^+-ion pumps, anti-apoptotic, DNA damage repair, immunomodulatory, and EMT molecules that contribute DR to OSCC [96, 99, 129, 130]. Thus, the TME plays an influential role in the therapeutic resistance of OSCC.

2.7 General senescence escape

Senescence is an irreversible process of life. The cells gradually lose active cell division/ repair over time. Senescence cells activate tumor-suppressor p53 and p16INK4a molecules and pathways [131]. Many OSCC drugs trigger DNA damage/ breakage, oncogenic signaling, and telomere shortening [132]; hence aging becomes faster in cancer patients. Escape from therapy-induced senescence was known for tumor recurrence, CSCs, and therapy resistance [133]. The inhibitors of telomerase enzyme had sensitized the OSCCs with short telomeres to radiotherapy [134]. Resistance to radiotherapy was higher in the OSCC cells with a higher anaphase bridge index [134]. Sustained inhibition of PARP-1 affected therapy resistance in OSCC cells [133, 135]. p62-overexpressed cells showed increased senescence and autophagy in HNSCC [136]. The senescent cells observed with augmented Cdc2/Cdk1 activity promote survivin expression. Survivin inhibits apoptosis following chemotherapy and causes therapy resistance in OSCC [137-139]. Thus, the senescence escape contributes to therapy resistance in OSCC.

2.8 Heterogeneity of tumor

The oral tumor comprises a heterogeneous population of cells [140]. Types of heterogeneity include genetic, epigenetic, cell type [cancer cells, stromal cells, immune cells, etc.), metabolic (distribution of oxygen, nutrient, etc.), and temporal heterogeneity reported in dynamic tumor progression [141]. Oral tumor heterogeneity is a threat to treatment success [142]. After initial treatment, the clonal variants show different sensitivity levels to a particular targeted therapy. The new subpopulations evolve similarly to Darwinian selection with additional drug selection pressure. The drug-resistant tumor cells, with more heterogeneity, behave like CSCs [143]. Recently, multiple CD44 variants have added to heterogeneity, causing DR in OSCC [11, 144]. The heterogeneous tumor cells and surrounding TAF/TAM exchange exosomes, transfer miRNAs/circRNA/lncRNA, and induce DR [145, 146]. Heterogeneity increasing varying hypoxia and nutrition [147] have been associated with DR in OSCC. Finally, the OSCC heterogeneity support therapy failure.

2.9 Induction of EMT

EMT is a process when an epithelial cell progressively acquires a mesenchymal cell feature. These transformed cells acquire invasive, metastatic properties and are common to OSCC. The EMT and CSC share overlapping features. The DR oral cancer cells behave like oral CSC (OCSC) by activating the EMT program [11, 12]. Higher EGFR (epidermal growth factor receptor) signaling can back EMT, and therapy resistance in OSCC [148, 149]. Many EMT-targeting drugs contribute to therapeutic efficacy [150]. Further, the fibroblast growth factor-8 (i.e., FGF8), lncRNA MALAT1, miRs (miR-1252-5p/miR-3148, and miR-429) regulate EMT and DR in OSCC patients [151-154]. The therapy resistance and EMT-linked molecules (TGF-β, Wnt, and Snail/ Slug) are upregulated in resistant OSCC cells [62, 155-158]. Various EMT-linked TFs [159], like β-catenin, Snail, Slug, Twist, ZEB, and SRY box 4 [SOX4) [16, 65, 155, 160-164] persuade DR to

OSCC. The three Snail family members are Snail1/2/3 (or Snail, Slug, and Smuc) [155, 165], Twist [166-168], ZEB1/2 [169-171], p53 homolog p63 (ΔNp63) [172, 173] are involved in EMT, and DR in OSCC. The embryonic stem cells TFs Oct4, Sox2, and Nanog promote EMT and DR in OSCC [12, 174-178]. The miRNAs participate in EMT, and cancer DR [179-181]. miR-30a, miR-224-5p, miR-155, miRNA-619-5p, miR-371/372/372, miR-31-5p participate in different EMT and DR in OSCC [91, 93-97, 182]. Similarly, the miR-149-5p, miR-214-3p, and miR-1246 mediate chemoresistance [98, 102, 183, 184], whereas the miR-340-5p (of hypoxic tumor cell) offers radio-resistance [185], and miR-30a confers cisplatin-resistance in OSCC [96, 99]. Higher basal intracellular ATP [186, 187] and lactate dehydrogenase-A (LDH-A) [47, 188-190] promote EMT and offer DR. Hence understanding EMT/CSC can boost future anti-DR OSCC therapeutics.

2.10 Jigsaw extracellular vesicles/ microsomes

The extracellular (EVs) vesicles carry bio-signals (protein, nucleic acid, and lipids) that are utilized for cell-to-cell communication [191]. These lipid-bilayer-enclosed EVs are released naturally, contain biomolecular cargo, participate in intercellular communications, and endorse DR [192]. EVs can be exosomes (30–100 nm), microvesicles (100–1,000 nm), and oncosomes (1–10 μm) [129]. Recently, the DR mechanisms of exosomes and microvesicles were reviewed in OSCC [129]. These EVs carry miRNAs that promote therapy resistance [193]. The chemo-sensitive OSCC cells develop DR once they contact the exosomes released from DR cells [194]. EVs carry miRNAs (miR-338-3p-LIN28B, miR-196a, and miR-30a, like miR-21, miR-21-5p) causing cisplatin-resistance [13, 96, 195, 196], radio-resistance (miR-340-5p) [185] in OSCC. Further, the EVs released by CSC activate signal transduction (β-catenin, PI3K, Stat3, mTOR, TGF, and CAF) pathways of OSCC [146].

Exosomes released from DR tumor cells transform the sensitive tumor cells into DR [197]. Cisplatin levels can recruit copper efflux (ATP7A/B via ILV) transporters at the cell membrane [198], which offers DR in OSCC [198, 199]. The V-ATPases, expressed at a higher level in OSCC, change in/extracellular pH and participate in DR [108, 110, 200], and their inhibitors sensitize the DR OSCC cells [201]. Hence, vesicular acidification is a survival strategy for OSCC cells [201]. The extracellular pH of oral tumors is lower than in normal tissue [110] and supports DR in oral cancer [202]. Exosomes favor anti-apoptosis and support DR in OSCC [13, 15]. The release of caspase-3 [203, 204], the exosomes derived CAF [196], CAF-CM [196], and various miRNAs [13, 96] from EV confer chemoresistance in OSCC.

Tumor-derived exosomes interfere with the DNA repair pathways, causing DR. Many cancer drugs, including cisplatin, can form DSBs (DNA double-stranded breaks) [205, 206]. These DNA lesions get repaired via NER (nucleotide excision repair) pathway [206] or BER pathway (base excision repair) in OSCC [207, 208] released by the exosomes [209]. The exosomes carrying DNA repair enzymes promote chemoresistance [209] and radio-resistance in OSCC [210]. The immunomodulatory effects of EV (from monocytes/macrophages) advanced DR in OSCC [211, 212]. DNA synthesis interfering drug (cisplatin and doxorubicin) prevents the dividing of immune cells and weakens the patient's anti-tumor immunity. These exosomes carry miRNAs and regulate innate, adaptive immune responses in OSCC [13, 211, 212]. Immunomodulation by exosomes is critical for DR in OSCC [114, 213-215]. Exosomes confer DR in OSCC [216] and offer future solutions.

3. Strategies for fighting against therapy resistance OSCC

Therapeutic strategies to treat DR oral tumors need to be amended. Continuous failure in tackling DR OSCC suggests that the ongoing system to deal with resistant or recurrent tumors is erroneous. Using a single chemo-drug or targeting one pathway is not sufficient. Inventions of novel drugs take lots of time and energy. Identifying its application in mouth cancer clinical trials is more tedious. And finally, when the drug is implemented, it kills only the sensitive oral cancer cells. But the resistant minor population of malignant cells survives and proliferates to form a recurrent tumor [11, 12, 15]. Most chemo drugs/radiation therapies are toxic to healthy cells or destabilize the genome. The tumor cells develop efficient DNA repair mechanisms to avoid cell death. Hence searching and fighting against therapy resistance looks like a never-ending game.

The heterogeneity and complexity of OSCC, are extraordinarily high. Identifying each molecule/player and finding a strategy to combat DR appears extremely difficult. The lessons learned from these steps suggest that combinational therapies with multiple low-concentration drugs are wise choices. On the other hand, plant-based natural compounds can also open other options and provide a permanent solution. The ancient system of Indian medicine, or "OUSADHEYA", is based mainly on these plants or "VANASPATI". These were written in Ayurvedic texts, "Atharva Veda", and different Samhitas (like "Charak Samhita", "Sushruta Samhita", and "Vagbhata Samhita" [217, 218], could be tried to win over DR OSCC.

4. Natural compounds against drug-resistance OSCC

The plant-based natural compounds have been used for curing diseases for ages. Though single compound/s are widely used in research, crude extracts are more balanced. The synergistic effects of different compounds present in several plant extracts can regulate other enzymes, transporters, and signaling pathways. It can overcome DR, enhance pharmacological potency through drug-drug interaction, and improve bioavailability [219]. These whole

extracts of root, stem, and leaf are stable, and plants co-evolve with humans. Using the extracts/ formulations of different plants and animals will be wise to tackle DR OSCC. Here some critical observations of the various crude extract have been summarized in table 1. More research is needed to wisely use these for treating DR OSCC.

Besides the crude extracts, some natural/ natural-derived compounds have less toxic side effects than many cancer chemotherapy drugs. Plants produce secondary metabolites that have been well-recognized for their anti-cancer properties. These naturally occurring compounds are manufactured in nature's laboratory and are mostly non-

Table 1: Plant extracts and their successful application in drug-resistant oral cancer.

Sl No	Plant extract	Effect on oral cancer and drug-resistant oral cancer	References
1	*Azadirachta indica* A. Juss extract	The extract contains limonoids nimbolide, azadirachtin, and neem leaf glycoprotein. It has anti-tumor and DR properties against OSCC	[220, 221]
2	Areca nut extract	Though chewing areca nut (AN) triggers OSCC, AN extract (ANE) decreases cisplatin toxicity by inducing autophagy	[222]
3	Bitter melon (BM) extract	It inhibits the metabolism of lipids and glucose. Induces ER/ oxidative stress causing apoptosis in OSCC	[223]
4	BMEVs	Extracellular vesicles derived from BM (BMEVs) decrease the 5FU resistance of OSCC	[224]
5	*Centella asiatica* extract (with Asiatic acid)	Found to have anti-cancer activity in cisplatin-resistant HNSCC	[225]
6	Celastrol (a pentacyclic triterpenoid) treatment	Celastrol (Chinese herbal medicine *Trypterygium wilfordii*) was found helpful in treating MDR oral cancers	[226]
7	Danshen extract	Danshen extract identified be a potential anti-cancer agent in DR oral cancer treatment	[227]
8	*Eruca vesicaria* extract	Its intake affects ABC transporters in liver cells. This could be beneficial in DR OSCC.	[228]
9	*Glycyrrhiza glabra* (Liquorice extract)	It contains secondary metabolites. It is used in foods, cosmetics, and medicines (anti-ulcerative, anti-carcinogenic, anti-microbial, and anti-DR in OSCC)	[229]
10	*Juniperus indica* extract	The extract synergizes with cisplatin to halt cell cycle progression and caspase activation	[230]
11	*Mangosteen* pericarp extracts	Shown cytotoxic effects on oral cancer	[231]
12	*Ocimum sanctum* extract	Reported causing a cytotoxic effect in oral and HNSCC. Inhibited MMP2/9 activity and can be used against DR OSCC	[232]
13	*Polygonum cuspidatum* extract	Induces apoptosis and autophagy in cisplatin-resistant human OSCC	[233]
14	*Plumbago zeylanica* L. (Plumbagin) extract	Effective against DR tongue SCC	[234]
15	Red Ginseng extract (a Korean herbal medicine)	Inhibits Pgp-mediated drug efflux and sensitizes chemotherapy resistance OSCC cells	[235]
16	*Scutellariae radix* (a Chinese herbal medicine)	Acts against chemoresistant human tongue SCC and promotes apoptosis	[236]
17	*Solanum nigrum* ripen fruit extract	The unripe fruit is a chemo-sensitizing agent against Adriamycin-resistant cancers and downregulates JAK1, p/Stat3, and Mdr1. It shows anti-tumor properties.	[237]
18	*Vernonia cinerea* Less (VC) extract	It inhibits multidrug resistance transporter in epithelial cancer cells.	[238]
19	*Vaccinium corymbosum* L. extract	Reserved the OSCC growth acted against PI3K/Akt, TGF-β, and NF-κB pathways.	[239]
20	*V. macrocarpon* (cranberry) extract	Upregulated the apoptosis, p53, and c-myc level in OSCC	[240]
21	*Withania somnifera* extract	It has anti-inflammatory properties (Ayurveda practice) and is also effective in treating DR cancers. Known for immune-modulatory and MDR and can reverse chemotherapy-induced effects.	[241, 242]

toxic to normal cells. These molecules are hard to design in a chemical laboratory, maintaining their specificity only for cancer cells. Natural compounds are highly demanded (WHO) in cancer treatment. These phytochemicals generally inhibit/disrupt methyltransferases, histone deacetylases, antioxidants, DNA damage, and mitosis promoters. Recently, these plant compounds with anti-DR oral cancer properties have been identified. These largely comprise brassinosteroids, polyphenols, and taxols. Polyphenolic compounds comprise curcumin, flavonoids, gallocatechin, resveratrol, and tannins. The different polyphenolic compound inhibits stemness [243] and drug transporter (ABCG2) in OSCC [244]. Many of them were used against OSCC to eliminate MDR cells [245], cisplatin-resistant [246], and oral CSC populations [247, 248]. The modifications of this nanotechnology cisplatin-resistant OSCC [249, 250]. Some other was useful against cetuximab resistance in HNSCC [251].

Similarly, the flavonoids have also shown DR properties and were more effective against OCSCs than normal cells [61]. Some flavonoids also inhibited cell growth and invasion/migration [252] and suppressed the formation of the DR sphere [63], down-regulated stemness signature/ self-renewal, and chemoresistance [253] in OSCC/HNSCC. The flavonoids sensitized HNSCC cells to cisplatin [254] and promoted anti-tongue tumor activity [255, 256].

In contrast, Brassinosteroids are steroid plant hormones and have anti-cancer properties in hormone-sensitive (breast and prostate) cancers [257, 258]. Recently the role of the female hormone on HNSCC [259], expression of ER-alpha in OSCC [260-262], and androgen/progesterone receptors with poor prognosis of OSCC [263] have been reported. Hence, Brassinosteroids could be effective against DR OSCC but needs investigation. Here some essential phyto-compounds and their effect on DR OSCC have been summarized in table 2.

Table 2: List of selected phytochemicals and their success story in drug-resistant oral cancer

Sl No	Phytochemical/s	Effect on Oral Cancer	References
1	Apigenin	Reduce CSC marker expression in HNSCC cells under hypoxia. Cetuximab-resistant HNSCC cells (with EMT) responded to apigenin treatment	[264, 265]
2	Brassinosteroids	The role of the female hormone ER-alpha androgen and progesterone receptors on DR OSCC was reported to open possibilities for many Brassinosteroids compounds.	[257-259, 260-263]
3	Curcumin	Curcumin inhibited OSCC tumorigenesis, including DR. Curcumin nanoparticles triggered apoptosis in CR-OSCC.	[250, 266]
4	Doxorubicin	Treated as chemotherapy, electrical impulse chemotherapy (EIC) against and found effective in chemotherapy resistance OSCC. Nano micelles carrying Doxorubicin eliminate multidrug resistance (MDR) cells in OSCC.	[255, 267-269]
5	Epigallocatechin gallate (EGCG)	EGCG inhibits drug transporter ABCG2 in OSCC. EGCG also sensitized MDR OSCC cells and cisplatin-resistant OSCC cells and eliminated OCSC.	[244-247]
6	Genistein	A combination of genistein (protein tyrosine kinase inhibitor), along with other anti-cancer agents, had augmented cytotoxic effects in CSC/ drug-resistant OSCC cells	[270]
7	Honokiol	Honokiol was found to overcome cetuximab resistance and chemosensitizing effect in OSCC.	[251, 271]
8	Isoliquiritigenin	Isoliquiritigenin was more potent against OCSCs than normal cells.	[61]
9	Isothiocyanate (mustard oil)	Isothiocyanate inhibited cellular proliferation and induced apoptotic pathways in human cisplatin-resistant oral cancer cells.	[272]
10	Kaempferol	Kaempferol sensitized HNSCC cells to cisplatin drugs	[254]
11	Magnolol	Magnolol inhibits the stemness property of OSCC	[243]
12	Nimbolide	Nimbolide was beneficial in eliminating DR OSCC cells. It irradicated cisplatin-resistant human OSCC when treated with Bcl-xL/Akt antagonists.	[14, 15]
13	Pterostilbene	The pterostilbene inhibited MDR1 expression in OSCC and can be used against DR cancer.	[248]
14	Podophyllotoxin	Eradicate therapy-resistant HNSCC cells	[273]
15	Quercetin	Quercetin inhibited cell growth, invasion/migration, colony-formation, and sphere-forming potential in DR OSCC. The combined effect of quercetin and cisplatin promotes apoptosis in OSCC.	[63, 252, 274]

16	Resveratrol	The resveratrol acts against cisplatin-resistant and Cetuximab-resistant OSCC cells. It reduced the invasiveness of cisplatin-resistant OSCC.	[249, 275, 276]
17	Silibinin (milk thistle seeds)	Silibinin down-regulated the chemoresistant, stemness, and self-renewal in HNSCC.	[253]
18	Sulforaphane (SF)	SF phytochemicals from broccoli possessed anti-stemness/DR OSCC properties targeting SOX2/OCT4.	[12, 277]
19	Ursolic acid	Ursolic acid decreases Akt/BAD signaling and promotes cell death in cisplatin-resistant oral cancer cells	[278]
20	Vicenin-2	Vicenin-2 (a bioactive compound in *O. sanctum*) application improved antioxidant levels, lipid peroxidation, and pro-inflammatory cytokines and halted DMBA-induced hamster oral carcinogenesis	[279]

Table 3: Commonly affected pathways after treatment with plant-based phytochemicals in drug-resistant oral cancer cells

Effects of Plant Extracts	Cellular pathways/ molecules targeted in drug-resistant oral cancer cells	References
Antioxidant effects	The plant products have a scavenging effect on free radicals generated by ROS/ RNS. Many enzymes (nitric oxide synthases, xanthine oxidase, peroxidase) involved in the production of ROS/ RNS are inhibited by plant products. Plant phytochemical/ extract with metals promotes the metal-mediated reduction of peroxides in cancer/ DR cancer.	[280-283]
Effects on apoptosis	Plant-based molecules induced cell death in DR cancer cells. The ROS level, post-translational modification/s, and impaired glycolysis promoted apoptosis via the activation of p53/Bcl-2/Bax/caspase-3.	[13-15, 277]
Inhibition of proliferation	The oral cancer DR forms a DNA adduct and thus blocks DNA replication causing cell cycle arrest. Cisplatin-resistant cells overcome this. Increased nucleotide excision repair (NER) such as ERCC1, epigenetic changes such as DNA methylation, and cancer stemness were reported in CR-OSCC. Recently, several plant compounds promoted cell cycle arrest in DR OSCC cells.	[12, 256, 284-287]
Retards the invasion and metastatic	Plant compounds (PC) suppressed the invasion/metastasis process. Deregulating several EMT-associated molecules (like β-catenin, E-cadherin, fibronectin, and vimentin), along with CSC genes, the PC decreases the metastatic potential. PC reversed EMT through signaling pathways (Akt/GSK3β/Snail and MAPK-ERK) and reduced the levels/ activity of MMP-9/-2 in DR OSCC.	[16, 17, 288]
Epigenetic effects	Phytochemicals can affect chromatin remodeling, DNA methylation, histone modifications, and miRNA regulation. Phytochemicals/ PCs also regulate HDACs, HATs (histone acetyltransferases), and DNMT1 (DNA methyltransferase-1) in DR OSCC cancer cells.	[17, 289, 290]
Eradicating CSCs	Drug resistance and CSCs have overlapping functions. Many CSC genes are expressed in DR cells, such as Oct4, Nanog, Sox2, and CD44. Plant-based phytochemicals reduce stemness, as reported in DR OSCC/ OCSC.	[11-14]

5. Effects of plant-based products on drug-resistant OSCC cells

Plant-based products/formulations for treating cancer patients have been used for a long. The anti-cancer effects of many plant-based extracts/molecules were discussed in the previous sections (tables 1 and 2) on DR OSCC cells. All these products act as an antioxidant, triggers apoptosis, inhibits proliferation, retards invasion/ metastatic, affects epigenetics, or destroy CSCs, and can eradicate DR OSCC cells. These agents affect several pathway/s and benefit DR OSCC, as summarized in table 3.

6. Management of drug-resistance OSCC patients

The DR OSCC showed high heterogeneity, and various non-/genomic changes make these cells challenging to treat. Hence it is high time to identify these regulators of DR of OSCC. Recent advancements in high throughput cancer genomics, proteomics, and metabolomics have identified many of these regulators at the individual patient level.

Since the causes of DR causes vary from patient to patient, personalized treatment strategies can benefit individual patients [291]. A continuous follow-up of the resistance tumor and patients' health is important. The tumors, not the patients [except metastatic cases), should be treated locally. A cocktail of low-dose chemotherapeutic/targeted drugs can target multiple proteins, enzymes, receptors, RNAs (miRNA, lncRNA, or circRNA), and pathways that eliminate DR cells. These low-dose and/or fluctuating drug concentration combinations could benefit OSCC patients. The highest drug dose was tolerated (adaption and

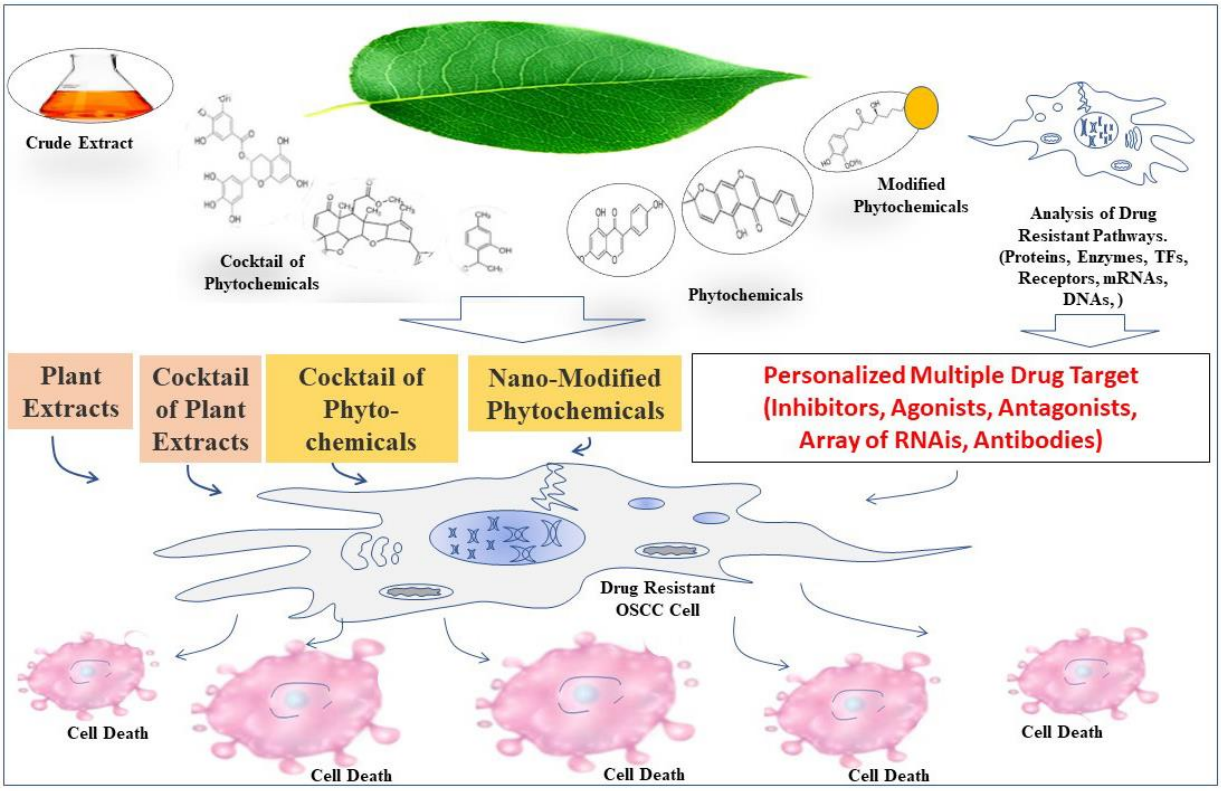

Figure 3. ***Management of drug-resistant OSCC patients.*** Treatment of DR patients can be improvised. The personalized drug can be designed based on the high throughput cancer genomics, proteomics, and metabolomics study at the individual patient level. These targeted drugs aim at numerous proteins, enzymes, receptors, and RNAs of the DR pathways. The plant-based anti-cancer formulations combining different plant extracts, a patient-specific formulation/ cocktail of multiple phytochemicals, polyphenol/s, and antioxidant/s, can be used along with a cocktail of low doses of targeted drugs to kill DR OSCC.

mutations) by cancer cells developing DR. Novel treatment strategies of high drug dose (DD) followed by low-DD/ no-DD followed by moderate-DD can bring delayed DR [292]. One of the critical strategies for overcoming DR could be to block the energy supply of OSCC cells. All living cells, including tumor cells, need the energy to survive. To support the actively dividing cell, the energy demand of a tumor cell is maximum [293]. Healthy cells are more flexible in selecting their energy source but not the DR-OSCC. Hence the deprivation of glucose with glucose transport/ glycolysis enzyme inhibitor/s and cocktail drug may be effective. In/extra-tumoral ATP is a crucial TME molecule that impacts OSCC cells for DR [293]. Specific inhibition of ATP synthesis and degradation of extracellular ATP can boost DR tumor therapy. Other strategies among the ten DR-OSCC plans proposed earlier could also be promising.

Finally, there should be more focus on plant-based anti-cancer formulations. Often the whole plant extract or a part of the plant extract (table 1) works better. Thus, either individual (single) plant extract or a combination of different plant-based formulations can be tried on DR OSCC cells/ patients. Furthermore, individual phytochemicals can act and sensitize the DR oral tumor cells [11, 12, 14, 15, 294, 295]. A cocktail of different phytochemicals (table. 2) can be formulated and tried with routine treatment procedures. The efficacy of all these plant-based treatments can be monitored based on the cell biomarkers explained in Table 3 and based on the result/s, treatment amendment can be adopted. All these approaches can act on multiple pathways (figure 3) and have a higher chance of eliminating DR OSCC.

7. Conclusion

In conclusion, the recent picture of therapy resistance to OSCC seems grim. These highly evolved OSCC tumor cells get unlimited support from their TME and show high levels of heterogeneity, support each other, and desert almost every treatment plan. They are adaptive and flexible in changing their drug target, bioenergy, drug efflux, DNA repair, epigenetics, TME, senescence, heterogeneity, EMT, and cell-to-cell communication. These parameters could be looked at carefully in designing personalized therapy for OSCC. Hence no generalized synthesized drug treatment can be very effective in the long run. Instead, the plant-based formulations seem to be more promising and show hope. These drugs/ phytochemicals should be improvised with recent technology [296] to improve their efficacy. Lastly, understanding the tumor/ patient-specific need to overcome drug resistance is key to success.

Declarations

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