Review Article

Potential benefits of novel agent Tanshinone in the management of oral submucous fibrosis

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ABSTRACT

Oral submucous fibrosis (OSMF) is a chronic insidious disease characterized by difficulties in mouth opening and tongue movement, burning sensation and fibrosis of the oral mucosa leading to dietary restrictions, impaired speech, and difficulty in maintaining oral health. Several factors may attribute to the disease that include areca nut chewing, genetic predisposition, immunologic processes, consumption of chillies and nutritional deficiencies. Currently many treatment modalities for OSMF are available with varied results such as antioxidants, vitamins, corticosteroids, peripheral vasodilators, enzymes and surgical procedures. However, no single therapy can completely relieve the symptoms of OSMF. Therefore, identification of an effective treatment modality for OSMF is necessary. The current review article highlights the potential benefits of the novel agent tanshinones (TSNs) in the management of OSMF.

Key words: *Anti-cancer, Oral submucous fibrosis, Oral squamous cell carcinoma, potentially malignant disorder, tanshinones*

Oral submucous fibrosis is defined as "An insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. It is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic changes of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to speak" [1]. Although exclusively seen in Indians and Southeast Asians, lately cases have been reported worldwide like Kenya, China, UK, Saudi Arabia and other parts of the world where Asians have migrated and are migrating**.** It has been observed that among Indians and Southeast Asians, 0.2-1.2% of an urban population attending dental clinics are affected by OSMF. Among Indian population, the prevalence of OSMF is 5% in women and 2 % in men, most commonly seen in patients between ages of 20 and 40 years. Malignant transformation rate of OSMF was found to be in the range of 7-13% and incidence over a 10 year period is 8% [2]. According to long-term follow-up studies, a transformation rate of 7.6% over a period of 17 years was reported [3].

Many researchers have proposed various treatment modalities for OSMF such as antioxidants, vitamins, alpha lipoic acid, corticosteroids, peripheral vasodilators, enzymes, lasers, ultrasound, physiotherapy and surgical procedures. Although many treatment modalities have been advised and tried, yet no single therapy can completely relieve the symptoms of OSMF. Therefore, identification of an effective treatment modality for OSMF is necessary. Currently, there is much interest in exploring compounds extracted from natural products to treat OSMF and oral cancer. Natural products have additive effects when used in combination with chemotherapeutic agents and radiotherapy. In addition to the well-studied cardiovascular activities, tanshinones (TSNs) have been investigated more recently for their anti-cancer activities in

vitro and in *vivo*. among various types of cancers, such as breast, colon, prostrate liver, and leukemia.

TSNs are a class of abietane diterpene compound isolated from *Salvia miltiorrhiza* which is known as Danshen or Tanshen in Chinese (Figure 1**) [**4**]**, a well-known herb in Traditional Chinese Medicine (TCM). Since they were first identified in the 1930s, more than 40 lipophilic tanshinones and structurally related compounds have been isolated from Danshen. The compound is mostly used in China and many Asian countries as preventive or therapeutic remedies for coronary heart diseases, vascular diseases, stroke, hyperlipidemia, endangiitis, arthritis and hepatitis. The class of Tanshinones includes compounds such as cryptotanshinone (CT), tanshinone IIA (TIIA), tanshinone I (TI), dihydrotanshinone I (DH-TI), isotanshinone I, tanshinone IIB, methyltanshinone, isocryptotanshinone I, isocryptotanshinone II, etc [5].

Figure 1: Salvia plants and roots [4]

MECHANISM OF ACTION

The various compounds of tanshinones have varying characteristics. TI inhibits cancer cell proliferation and induces apoptosis. TIIA induces differentiation of cancer cells and has antiangiogenic activities. Depending upon the concentration, TIIA induces antineoplastic activities such as cell-cycle arrest and caspase dependent apoptosis by interference in mitosis, increase in reactive oxygen species, and cellular ca2+. Cryptotanshinone has antiproliferation and proapoptosis properties against various cancer cells through cell-cycle arrest and apoptosis. It inhibits signal transducer and activator of transcription 3 (STAT 3). DH-T1 is potent among the TSNs and exerts its anticancer effects through cell cycle arrest and apoptosis. TSNs inhibit adhesion, migration, invasion, and metastasis of cancer cells; modulates inflammatory and immune response; inhibits telomerase; interacts with DNA minor groove and activates p53, thereby inducing apoptosis; modulates androgen receptor pathway; and sensitizes cancer cells to chemotherapy and radiotherapy [6]. Different pharmacological actions of TSNs have been depicted in Figure 2 [7].

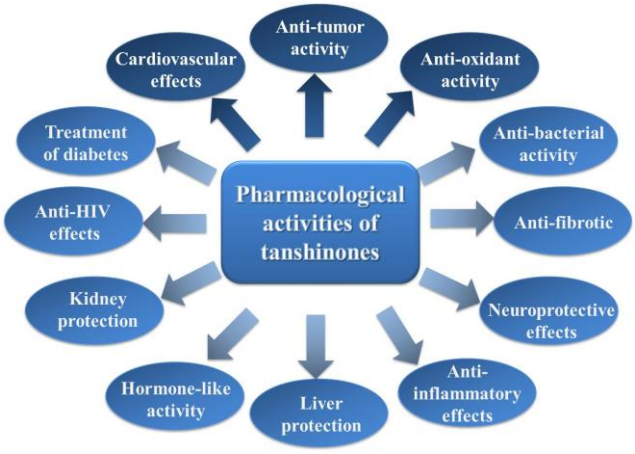

Figure 2: Pharmacological activities of tanshinones [7]

TANSHINONES AND OSMF

Zheng et al. examined the inhibitory effect of TSN on progression of OSMF. The authors found that TSNs inhibit arecoline mediated proliferation of primary human oral mucosal fibroblast and reversed the promotive effects of arecoline on epithelial–mesenchymal transition (EMT) process Oral mucosal tissues in OSMF have extremely low p53 when compared with normal tissues. Arecoline reacts with oral mucosal fibroblasts resulting in reduction of p53 and its related downstream molecules p21, Bax, and p53 upregulated modulator of apoptosis (PUMA) [8]. Arecoline promotes the hypermethylation of promoter of p53, which was reversed by TSN. In G1-S phase cell cycle, the repair of damaged DNA is facilitated by p53 protein. Along with this, p53 also hampers the cell from entering S phase and may prompt the damaged cells to undergo apoptosis [9].

Arecoline significantly upregulates lysine-specific demethylase (LSD1), but this effect is nullified by TSN. It

should be known that knocking down LSD1 results in increased p53 levels in presence of arecoline. TSN inhibits LSD1. Arecoline decreases E-cadherin expression but increases N-cadherin and vimentin expression in oral mucosal fibroblasts. TSN reverses these effects of arecoline in dose-dependent manner. TSN is known to decrease tumor growth of oral carcinoma *in vivo*. It is suggested that TSN decreased the expression of proliferative marker Ki67 in tumor sections of SCC-9 xenografts [8]. They also inhibit invasion and metastasis of cancer cells by altering matrix metalloproteinases [10]. TSN is synergistic with anticancer drugs, such as cisplatin, 5-fluorouracil, doxorubicin, and arsenic trioxide [11].

Tseng et al explored the anti-proliferative effects and mechanism of action of TIIA in OSCC KB cells. They observed that TIIA inhibited cell growth and induced apoptosis in oral cancer KB cells. A total of 90% of KB cells were killed on administration of 25 μg/mL TIIA for 72 h. TIIA caused cell death by inducing cell-cycle arrest at G2/M phase and apoptosis. Significant apoptosis of KB cells occurred when they were subjected to 10 μg/mL TIIA for 48 h or 20 μg/mL TIIA for 24 and 48 h. TIIA also induced loss of mitochondrial membrane potential, which resulted in cytochrome *c* and other apoptosis molecules release on being subjected to various stimuli. TIIA caused activation of caspase-3, caspase-9, and Poly ADP-ribose polymerase (PARP) [12].

Thus, TIIA appears to target the errors in cell-cycle regulation of cancer cells and is useful as an anticancer agent to control tumor growth [12]. Similarly, Ding *et al* investigated the radiosensitizing effects of TIIA on human OSCC. The authors observed that TIIA significantly sensitized SCC090 OSCC cells to radiation through enhanced reactive oxygen species generation and autophagy. The levels of three important autophagy proteins Beclin 1, Autophagy related 5 (Atg5), and Light chain (LC3-II) increased in the cells on treatment with TIIA [13]. All the above mentioned studies suggest that TSN and its components are the promising agents that could be potentially used in intervention against OSMF and OSCC.

CHEMICAL MODIFICATION OF TANSHINONES

Since TSNs possess high hydrophobicity, poor solubility in aqueous medium and poor oral bioavailability, these properties have been the major challenges for pharmaceutical development. Early effort in China with structural modification lead to the development of a water-soluble sodium TSNs IIA sulfonate (STS) which is widely used for patients with cardiovascular disorders [14]. However, this compound had little apoptosis-inducing ability when tested in six cancer cell linesm [15]. For this reason, investigators synthesized a novel TIIA compound, acetyltanshinone IIA (ATA). ATA exhibits increased water solubility and stronger apoptotic activity on multiple cancer cell lines than TIIA. ATA displayed higher growth inhibition ability on breast cancer especially ErbB-2/HER2/Neu positive cancer cells than normal cells [16].

CONCLUSION

Anticancer potential of tanshinones is through anti-proliferation, pro-apoptosis, anti-angiogenesis, induction of differentiation, and inhibition of adhesion, migration, invasion and metastasis. The inhibitory actions are through modulating the inflammatory and immune responses by inhibiting enzyme telomerase, interacting with DNA minor groove and activating p53 tumor suppressor, or regulating Androgen receptor or STAT3 pathways. Identification of AR pathway as a target of selected TSN provides scientific basis for developing new tanshinone based agents for various cancers in the future. One challenge is the poor water-solubility and oral bioavailability of natural tanshinones. However, chemical modification have resulted in improved water solubility, thus enhancing the anti-carcinogenic effect.

Although there are very few studies conducted on effects of TSNs in OSMF and OSCC till date, yet all of them have yielded positive results. Hence, TSNs appear to be promising in the management of OSCC and OSMF. Further clinical trials should be carried out to ascertain the benefits of TSNs in OSMF and OSCC patients.

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