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Gugulipid, an Extract of *Ayurveda* Medicine Plant *Commiphora Mukul* as a Potent Agent for Cancer Chemoprevention and Cancer Chemotherapy

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Abstract

Gugulipid (GL), an extract of *Commiphora mukul,* has been safely used for thousands of years in the Indian Ayurveda medicine practice for the treatment of different ailments and has been used recently in many clinical trials that focused on its cholesterol-lowering effect. GL has recently been paid great attention for its cancer chemopreventive and chemotherapeutic potential. Z- and E-Guggulsterone have been identified as the major active components of GL. Studies have shown that GL as well as Guggulsterones can inhibit cancer growth *in vitro* and *in vivo* and lead to prevention of cancer initiation, promotion and progression. Although the action mechanisms of GL are not completely understood, GL has been revealed as a multitargeted cancer chemopreventive and chemotherapeutic agent. The increased understanding of the anti-cancer activity of GL and its molecular targets would allow us to improve its efficacies in different types of human cancers by single and/or combination strategies.

Keywords: Gugulipid; Guggulsterone; Cancer chemoprevention; Guggul plants

Gugulipid (GL, guggul, guggal, or gugul lipid) is the ethyl acetate extract of gum guggul resin (raw material) that is harvested directly from the *Commiphora mukul* tree (family name: Burseraceae; synonyms: Hook, Bandari, *Balsamodendron mukul*, and *Commiphora Wightii*). GL is a highly valued botanical medicine. As aforementioned, GL has been safely used for thousands of years in the Indian Ayurvedic medicine for the treatment of different ailments, including lipid disorders, rheumatoid arthritis, ulcers, osteoarthritis, bone fractures, epilepsy and obesity [1-5]. In 1986, GL was granted approval in India for marketing as a lipid lowering drug (Indian Pharmacopeia 2007: pgs. 2038-2040). Several products of standardized formulations of *Commiphora mukul* are already in human use as cholesterol-lowering agents [1-4]. The Z- and E-forms of guggulsterone (Gug, 4,17(20)-pregnadie-3, 16-dione) have been identified as major active components of GL [1-4]. GL and its active component z-Gug have been used in many clinical trials that focused on its cholesterol-lowering effect [1-7]. Numerous studies continue to support that many edible phytochemicals have cancer chemopreventive and chemotherapeutic potential [8,9]. These finding motivated the investigation of the cancer chemopreventive and chemotherapeutic potential of GL and its active components.

The evidences of the anti-cancer activity of Gugs were provided by us and other laboratories [10-21]. We, for the first time, investigated the inhibitory effect of Gug on the growth of the human prostate cancer cells [10,11]. The results has shown that Gug significantly inhibits the proliferation of PC-3, LNCaP and DU145 human prostate cancer cells, but not a normal human prostate epithelial cell line PrEC [10,11]. The Gug-mediated suppression of cancer cell proliferation has also been reported in human breast cancer cells [12,13], head and neck cancer cells [14], leukemia cells [15,16], lung cancer cells [16], skin cancer cells [17], and colon cancer cells [18]. Gug treatment inhibited angiogenesis *in vitro* and *in vivo* to block colon and prostate cancer growth [18,19]. Based on these data, we hypothesized that GL might be more effective in growth inhibition of prostate cancer cells because it contains a number of steroids, including the two isomers Z- and E-Gugs. Therefore, we investigated the anti-cancer potential of GL in human prostate cancer cells [20]. Our data, for the first time, showed that GL has a stronger anti-cancer potential in human prostate cancer cells as evidenced by inhibition of cell growth compared with Z-Gug, one of its active constituents. A statistically significant inhibition of cell survival by GL was evident at IC_{50} ~ 1 μmol/L concentrations standardized to z-Gug. The effect on growth inhibition by GL was ~10-fold stronger than that of z-Gug [20]. Interestingly, a normal prostate epithelial cell line PrEC was significantly more resistant to growth inhibition by GL compared with prostate cancer cells [20]. Based on these results, we have arrived at the following conclusions: (a) GL treatment decreases the survival of human prostate cancer cells irrespective of their androgen-responsiveness, (b) a normal prostate epithelial cell line is significantly more resistant to growth inhibition by GL, and (c) uncharacterized constituent(s) of GL may interact additively or synergistically to inhibit viability of human prostate cancer cells [20]. It is reported that treatment with GL (3 μmol standardized to z-Gug, daily for 3 weeks) resulted in the enhancement of cetuximab activity in the xenograft model of head and neck cancer [21].

Although the mechanisms of the anti-cancer action of GL are not completely understood, these studies have indeed indicated that GL and its active components (Gugs) inhibit cancer cell viability by causing apoptosis [10-14,16,17,20-25]. The mechanisms underlying GL-induced apoptosis are involved in the change of Bcl-2 gene family proteins [10,11,16,17,20], inhibition of NF-kB signaling [12,16,17,22], regulation of MAPK pathways [11,17,20], suppression of farnesoid X receptor [25] and the bile acid receptor [26], and the inhibition of EGFR-STAT3 signaling [14,21]. The results implicate the involvement of STAT3 and VEGF/VEGFR signaling pathways in the regulation of GL-mediated anti-angiogenesis activity [18,19]. Tumor-specific induction of oxidative stress is expected to offer a powerful therapeutic modality. In fact, many anticancer agents and naturally occurring and synthetic agents exhibit antitumor activity via ROS-dependent activation of

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apoptotic cell death. Our results indicate that the cell death caused by GL in human prostate cancer cells is triggered by ROS generation [20]. This conclusion is based on: (a) GL treatment caused a dose- and time-dependent ROS production in LNCaP and C81 cells; (b) GL-mediated ROS generation and apoptotic cell death were significantly attenuated by antioxidant NAC; and (c) the same treatment with GL did not affect the ROS induction and cause apoptotic cell death in PrEC. It was also reported by us [10,11] that ROS is indispensable for z-Gug, one of the important active components of GL, caused apoptosis in human prostate cancer PC-3 cells.

Even though pharmacokinetic parameters for GL have not been determined in humans, the maximal plasma concentration of z-Gug (C_{max}) in rats was shown to be 3.3- and 18.3 μmol/L following oral gavage with 50 mg z-Gug/Kg body weight and intravenous injection with 18 mg z-Gug/Kg body weight [27]. Based on these pharmacokinetic observations, it is possible that the concentrations of GL (1 μM) needed to inhibit cancer cell growth may be achievable in humans.

The studies reveal that GL is a potent inhibitor of cancer cell growth. GL is a multitargeted chemopreventive and chemotherapeutic agent. Future studies on GL should focus on: (a) the study of pharmacokinetics and bioavailability; (b) the *in vivo* study using xenogrfts, transgenic models and angiogenesis models as well as orthotropic models; and (c) the identification of biomarkers of GL response potentially useful in future clinical trials and in the optimization of GL-based regimens for prevention and therapy of cancer.

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