Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Therapeutic use of Guggulsterone in COVID-19 induced obesity (COVIBESITY) and significant role in immunomodulatory effect

L. Preethi, Nila Ganamurali, Dhivya Dhanasekaran, Sarvesh Sabarathinam *
SRM College of Pharmacy, SRM IST, Kattankulathur, Kancheepuram, Tamil Nadu, India

ABSTRACT
COVID-19 has emerged as a major cause of health crisis around the world. Psychosocial, Behavioral and metabolic changes especially weight gain, among variety of population was produced in this pandemic, through variety of mechanisms. Hyperlipidemia is one of the major issues that result in serious cardiovascular complications. Governmental strategies to minimize the spread of COVID-19 through closures, lockdowns, and alterations in social interaction have complicated weight management efforts. And immunity being the need of the hour has to be improved to prevent the infection. Guggulsterone (GS) isomers are major bioactive compounds present in Commiphora mukul and Commiphora wightii. Guggulsterone shows anti-hyperlipidemic, anti-oxidant, anti-inflammatory, immunomodulatory and appetite regulating activity due to its peculiar characteristics. On the basis of clinical evidence, Guggulsterone seems to possess good cholesterol lowering, appetite regulating as well as immunomodulatory activity which can be beneficial during the pandemic of COVID-19.

1. Introduction
Cardiovascular complications are one of the global leading causes of concern due to the rising prevalence and consequence of morbidity and mortality with increasing economic crisis throughout the world (Amini et al., 2021). Complementary and alternative Medicine (CAM) therapies are widely practiced by majority of the cancer patients, asthma patients and diabetes patients (Anbari & Gholami, 2015). Herbs are widely used as alternative medicines for the management of asthma and diabetes, since patients are not satisfied with existing therapy (Sarvesh et al., 2018). Herbal preparations have been widely used in the management of hyperlipidemia, obesity as well as immunity such as Momordica charantia (for lipid lowering), Coleus forskohlii (weight reduction), C. fistula fruit pulp (used as immunomodulator) and many more (Majeed et al., 2021; Sharma et al., 2021; Thomford et al., 2021). Majority of the patients choose alternative medicine because it is harmless and easily available. Intentional use of CAM is related to positive attitudes, trustworthiness, and high-quality studies within the CAM-patient-setting (Kristoffersen et al., 2018). In accordance with the evidences from ancient Indian traditional system of medicine, Guggulu has a long history of use in Ayurveda for its lipid lowering activity. Guggulsterone is an Oleo-gum resin obtained from the stem branches of Commiphora species like Commiphora mukul, Balsamodendron mukul and Commiphora wightii and belongs to the family of Burseraceae. Guggulsterone is one of the major bioactive compounds that play a major role in lowering cholesterol (Sabarathinam & Vijayakumar, 2021).

Guggulsterone isomers upregulate the bile salt export pump (BSEP), an efflux transporter responsible for removing cholesterol metabolites and bile acids from the liver (Wu et al., 2002). E-guggulusterone is 16-dehydropregnenolone acetate. The presence of Ketone group in 17th position increases the lipid lowering activity by inhibiting the Farnesoid X receptor. Z-guggulusterone is 16,17-epoxypregnenolone where there is replacement of methyl and hydrogen group vice versa in the position of E-guggulusterone, which is to reduce the toxicity (Ham et al., 2011). It has also shown its effectiveness in regulating appetite and thus reducing weight which can be used as a swift and effective management for Covibesity. Immune boosting capability of guggulsterone is also worth noticing, as it can help in controlling cytokine storm which is one of the major inflammatory response to SARS-CoV-2.

1.1. General description of Guggulsterone
Guggulsterone is C21H28O2 and the IUPAC name is (8R,9S,10R,13S,14S)-17-Ethylidene-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15-
Phytochemicals in Guggul: A natural source of pharmaceutical compounds

L. Preethi et al.

Obesity Medicine 24 (2021) 100346

Fig. 1. Chemical structure of Guggulsterone.

Table 1
ADMET parameters of Guggulsterone.

| Parameters                        | Guggulsterone |
|----------------------------------|---------------|
| Water solubility (log mol/L)     | -4.931        |
| CaCo2 permeability (log Papp in 10⁻⁶ cm/s) | 1.294        |
| Intestinal absorption (% Absorbed) | 99.655        |
| Skin Permeability (log Kp)       | -2.465        |
| VDrs (Human) (log L/kg)          | 0.158         |
| Fraction Unbound (Fu)            | 0.001         |
| Substrate                        | CYP3A4        |
| Total clearance (log ml/min/kg)  | 0.61          |
| AMES Toxicity                    | NO            |
| Oral route Acute Toxicity (LD50) (mol/kg) | 1.843        |
| Oral route chronic toxicity (log mg/kg bw/day) | 1.769        |
| Hepatotoxicity                   | YES           |
| Skin sensitization               | NO            |
| Minnow toxicity (log mM)         | 0.312         |

Table 2
Toxicity profile of Guggulsterone predicted via OSIRIS Property Explorer program.

| PARAMETERS          | Guggulsterone (scores) |
|---------------------|------------------------|
| Mutagenic           | GREEN                  |
| Tumorigenic         | GREEN                  |
| Irritant            | GREEN                  |
| Reproductive effect | RED                    |
| TPSA                | 34.14                  |
| Drug likeness       | -0.31                  |
| Drug score          | 0.34                   |

decahydrocyclopenta [a]phenanthrene-3,16-dione with molecular weight of 312.45 g/mol (Girisa et al., 2020). The chemical structure of Guggulsterone is given in Fig. 1. Guggulsterone isomers are obtained from the resins of Guggulu, from the stem branches of Commiphora species like Commiphora mukul, Balsamodendron mukul and Commiphora wighti and belongs to the family of Burseraceae. Gugglu contains numerous phytochemical components such as steroids, Guggulsterone, Phytoester, Triterpenoids, volatile oil, Sesquiterpenoids, Diterpenoids etc. pkCSM online server was used to generate the Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) profile of Guggulsterone (Sabarathinam & Vijayakumar, 2020). The Pharmacokinetic profile of guggulsterone is given in Table 1.

Toxicity is accountable for the withdrawal and failure of new chemical entities. The toxicity profile of selected drugs was analyzed through the OSIRIS® Property Explorer program. This tool is accessible through cheminformatics. ch and chemistry.org. It is a freely available online software program that forecasts potential side effects such as mutagenicity, tumorigenicity, irritant, reproductive effects, drug-likeness and physicochemical properties analogous with a compound in a color-coded format. Green color indicates drug conform behavior, yellow indicates medium risk, whereas red color shows a high risk for mutagenicity or low intestinal absorption. These predictions are essential to prevent deleterious substances to advance in drug discovery and development. We have also compared certain drug-related parameters such as Topological Polar Surface Area (T.P.S.A.), drug-likeness and overall drug score (Ayati et al., 2012; Rashid, 2020; Osman et al., 2021).

OSIRIS® Property Explorer program was used to predict the Toxicity profile of Guggulsterone and it is listed in Table 2.

(a) T.P.S.A. - Blood-brain barrier penetration and intestinal absorption are bioavailability-associated properties that are well correlated with T.P.S.A. and is calculated as the sum of the contribution of fragments, mainly O- and N- fragments are considered.

(b) Drug likeness- A fragment-based approach is used for estimating drug-likeness via OSIRIS program. A positive value demonstrates that the study compound contains those fragments which are found in commercially available formulations.

(c) Overall drug score - This is calculated using criterions such as drug-likeness, molecular weight, toxicity risk, log S and log P values. A score of >0.5 along with minimal toxicity risk is considered favorable.

The ADMET profile of selected bioactive compounds can be generated from online accessible databases like the pkcsm server (http://biosig.unimelb.edu.au/pkcsm/prediction) OSIRIS® Property Explorer program. The canonical smile of selected bioactive was identified from the PubChem online database. The canonical smiles can be applied in the pkcsm server online database (step 01), followed by entering the ADMET option (step 02) to predict the selected compound’s entire pharmacokinetic profile.

OSIRIS® Property Explorer (www.cheminfo.org) is used to estimate the compounds’ drug-likeness and drug toxicity profile. By drawing the fine chemical molecule structure in the left side column, drug toxicity profile and drug-likeness can be measured easily. Step by step graphical representation is given in Fig. 2.

1.2. Use of Gugglu as an adjuvant therapy in COVID

COVID-19 is highly contagious with rapid human-to-human transmission. The common signs and symptoms of COVID-19 infection are cough, fatigue, fever, headache and some individuals reported with breathing difficulties such as shortness of breath and respiratory distress. Patients also report lung disturbances, reduced platelet count and reduction in circulation lymphocytes. A recent research indicated that 4% of the population under study had incidence of acute kidney injury in which the in-hospital mortality rate was found to be 20%, 33% and 90% in stage 1, 2 and 3 of acute kidney injury respectively (Paek et al., 2020).

COVID-19 induces overproduction of cytokines and leads to cytokine storm resulting in hyperinflammation, eventually causing multiple organ damage (Dariya and Nagaraju, 2020). The cytokine pathway is given in Fig. 4. Gugglu strengthens the immune system by means of anti-oxidant activity. The anti-oxidant activity is attributed to NF-E2 related factor 2 (Nrf2) that activates antioxidant response element (ARE)- driven expression of heme oxygenase 1 (HO-1) and other cytoprotective proteins (Almazari et al., 2011).

Guggulsterone containing products have such a long history in managing cardiovascular disease, including hypercholesterolemia and
atherosclerosis. Though discrepancies in experimental design, sample size, statistical review, and irrespective of race and ethnicity, an existing preclinical and clinical trials strongly support the therapeutic claims for guggul as mentioned in ancient Ayurveda. Some of the marketed products of Guggul are given in Table 3. We believe that guggulsterone plays a major role in lowering cholesterol, immunomodulation during pandemic and it would also be one of the best therapies for COVID pandemic induced obesity.

2. Antihyperlipidemic property

Isomers of guggulsterone have proved to be efficacious in lowering lipid levels as per various studies. Its lipid lowering activity is attributed to oxidative modification of low-density lipoprotein (Sabarathinam & Vijayakumar, 2021). It is also said to antagonize two nuclear hormone receptors involved in cholesterol metabolism which is also a possible reason for its antihyperlipidemic activity (Sastry et al., 2020). Anti-hyperlipidemic activity of guggulsterone is given in Fig. 3.

3. Appetite regulator

Health inequality has been a major part since time immoral. During this pandemic of COVID-19, the world has witnessed a surge in the biopsychological aspects than ever before. Studies have shown that the adverse mental burden linked to the COVID-19 pandemic might be associated with increased body weight in individuals (Pellegrini et al., 2020). Pellegrini et al. study witnessed the weight gain during the lockdown [Table 4]. Guggulsterone has shown great effects on weight loss (Orabi et al., 2020).

The anti-obesity activity of guggulsterone is attributed to the following.

---

**Table 3**
Different types of Marketed Formulations of guggulu.

| S.NO | Different types of Marketed Formulations of guggulu's |
|------|------------------------------------------------------|
| 1.   | Amrita Guggulu                                       |
| 2.   | AbhaGuggulu                                           |
| 3.   | Guggulwadi Vat                                       |
| 4.   | Kaishore Guggulu                                      |
| 5.   | Kanchanar Guggulu                                    |
| 6.   | LakshaGuggulu                                         |
| 7.   | Mahayograj Guggulu                                   |
| 8.   | NavaKguggulu                                          |
| 9.   | PanchikghritGgulu                                    |
| 10.  | Pathyadi Guggul                                      |
| 11.  | SambharkarGuggulu                                    |
| 12.  | SaptvinshtikaGgulu                                   |
| 13.  | TrayushanadGuggulu                                   |
| 14.  | VaradiGguguin                                         |
| 15.  | Yograj Guggulu                                        |

---

**Fig. 2.** Step by step graphical representation for estimation of ADMET parameters from pkcsm server and OSIRIS® Property Explorer program.

**Fig. 3.** Antihyperlipidemic activity of guggulsterone.
a. Direct activity on 3T3 L1 adipocytes that results in mitochondrial biogenesis, upregulation of UCP1 and cellular consumption of oxygen.
b. Adipocyte begins through M2 polarization and subsequent catecholamine release (Miller et al., 2019).

This pandemic seems evolving with time, so strategies must be developed to tackle COVIBESITY. And since guggulsterone proves to possess a great anti-obesity effect, we would recommend the use of guggulsterone isomers to the most vulnerable section of the society.

4. Immunomodulatory activity

“Immunity boosting” has been trending since the pandemic. Several herbal preparations have been implicated for improving immunity, since their bioactive components are acting as substantial warriors in this battle. Several species like Allium sativum, Cerasus avium, Berberis integerrima, Alceadigitata, Rubiatinctorum, Peganum harmala etc. were illuminated as ACE2 inhibitors, and are thus considered as immunomodulators after careful evaluation (Ziaei et al., 2009).

a) Inflammatory response by SARS-CoV-2

Increased levels of pro-inflammatory mediators and cytokines were found in patients infected with SARS-CoV-2, suggestive of a “cytokine

Table 4
Changes in weight and nutritional habits in adults with obesity during the “Lockdown” period caused by the COVID-19 emergencies.

| Author name and year | Methodology | Sample size | Outcome |
|----------------------|-------------|-------------|---------|
| [Pellegrini, 2020]   | Observational retrospective study | 164 patients were invited to participate in the survey, out of which, 150 patients who completed the questionnaire were included in the study. | Nearly 1.5 kg self-reported weight gain during the first month of lockdown. |

Fig. 4. Immune response (Cytokine storm) in COVID-19 patients.

Fig. 5. Anti-inflammatory and immunomodulatory activity of Guggulsterone through inhibition of NF-kB cells activation.
storm syndrome” (Miller et al., 2019). Since studies have shown that SARS-nCoV-2 activates NF-κB through various pathways leading to “cytokine storm syndrome”, immunomodulation at the level of NF-κB activation and IkB degradation along with inhibition of TNF-α will potentially result in a reduction of cytokine storm and alleviate the severity of COVID-19 (Harirhan et al., 2021).

b) Effect of guggulsterone on nf-kb signaling pathway

It has been demonstrated in various studies that guggulsterone shows anti-oxidant, anti-inflammatory activity through inhibition of the nuclear factor-xB (NF-κB) [Fig. 5], a key regulator for inflammatory responses. And thus, provides support to the immune fractions and also improves the defense mechanism of the body (Zhang et al., 2016). Studies have demonstrated such effects of guggulsterone. [Table 5].

5. Conclusion

Products containing Guggulsterone have shown great effectiveness in the management of hyperlipidemia, obesity as well as in improving the immune system. Since in-vitro studies on immunomodulatory effect of guggulsterone are very scarce, we recommended further research about these specific activities of guggul that can be helpful in pandemics such as COVID-19.

Funding

This research received no grant from any funding agency.

CRediT authorship contribution statement

L. Preethi: Methodology, Writing. Nila Ganamurali: Investigation, Resources. Dhivya Dhanasekaran: Data curation, Writing. Sarvesh Sabarathinam: Conceptualization, Writing - .

Declaration of competing interest

The authors declare no conflict of interest, financial or otherwise.

Acknowledgement

Sincere thanks to DR T M VIJAYAKUMAR, Department of Pharmacy Practice, SRM College of Pharmacy, SRM IST for constant motivation and support.

References

Almazari, I., Park, J.-M., Park, S.-A., Suh, J.-Y., Na, H.-K., Cha, Y.-N., Surh, Y.-J., 2011. Guggulsterone induces heme oxygenase-1 expression through activation of NrT2 in human mammary epithelial cells: PTEN as a putative target. Carcinogenesis 32 (2), 368–376. 10.1093/carcin/blr052. Carcinogenesis.

Amini, M., Zayeri, F., Salehi, M., 2021. Trend analysis of cardiovascular disease mortality, incidence, and mortality-to-incidence ratio: results from global burden of disease study 2017. BMC Public Health 21 (1), 401. 10.1186/s12889-021-10429-0.

Anbari, K., Gholami, M., 2015. Evaluation of trends in the use of complementary and alternative medicine health centers in khorramabad (west of Iran). Global J. Health Sci. 8 (2), 72–76. 10.5539/gjs.v8n2p72.
Zhang, J.-H., Shangguan, Z.-S., Chen, C., Zhang, H.-J., Lin, Y., 2016. Anti-inflammatory effects of guggulsterone on murine macrophage by inhibiting LPS-induced inflammatory cytokines in NF-κB signaling pathway. Drug Des. Dev. Ther. 10, 1829–1835. https://doi.org/10.2147/DDDT.S104602.

Ziaei, S.A., Heidari, M.R., Amin, G.R., Kochmeshki, A., Heidari, M., 2009. Inhibitory effects of germinal angiotensin converting enzyme by medicinal plants used in Iranian traditional medicine as antihypertensive. J Journal of Kerman University of Medical Sciences 16 (2), 134–143.