MEDICINAL PLANTS- ANTIOXIDANT PROTECTIVE AGENTS AGAINST OXIDATIVE STRESS, RADIATION AND VIRUS INFECTION

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Abstract
In this review, we strive to evaluate and provide sufficient evidence of the antioxidant and protective essence of classic herbs (*Silybum marianum, Curcuma longa Linn, Haberlea rhodopensis Friv*), used as dietary antioxidants, DNA modulating agents, metabolic radiation scavengers, hepatoprotectors, cancer treatment, and COVID-19 infection agents. The future use and development of effective herbal combinations require efficient non-toxic mixtures and conventional chemotherapeutics neutralizing systemic oxidative stress and predisposing to a reduced risk of developing cardiovascular, pulmonary, and neurodegenerative diseases, cancer, and etc.
Keyword: *plants, antioxidants, chemoprotection, COVID-19 infection*

Introduction
The most common causes of traditional herbal/plants remedies are for the treatment of chronic conditions and their perception as natural, safe and non-toxic (Watson and Preedy, 2008; Cohen, 2010). Herbal plants after treatment are taken as teas, syrups, essential oils, powders. The herbal or plant extract is extracted by alcohol tinctures, hot water extract, long-lasting boiled extract, root potions, etc.

Antioxidant protective agents against oxidative disorders, radiation-modulating effect, chemoprevention and virus infection of medicinal plants.
Since several studies, thousand synthetic anti-cancer chemicals have been described as caused hepatic impairment, followed by acute hepatic symptoms. The ineffective drugs metabolism led to liver transplantation cases or death (Pandit et al., 2012; Singh et al., 2015). Hepatocytes as primary metabolizing cells in the body carry out detoxification and elimination of xenobiotic and other medicals. Homeostatic dynamic equilibrium of the generation processes and ROS elimination and the prevention of oxidative disorders were also performed in liver (Zgheib and Branch, 2017). Efficacy of chemo-preventive plant antioxidants as therapeutic agents against drug-induced toxicity has been proven and widely used in Chinese and Indian traditional medicine. Saad *et al*. 2017 reported the pharmacological effects of herbal drugs and plants, used alone or in combinations, which act on synergistic antioxidant mechanisms, thereby neutralized the side effects of cellular ROS and have potential as a radioprotectors and cancer therapeutic agents. Plant-derived bioactive compounds provide antioxidant protection against ROS-mediated damages on DNA repair, carcinogen metabolism, scavenging free radicals, inhibition of cellular toxins, decreased angiogenesis and radiation- induced toxicity (Saad et al. 2017; Vallejo e al., 2017). The mechanism of damages to cellular biomolecules induced by ionizing radiation includes direct and indirect action the latter is mediated via ROS formation. Ionizing radiation has been involved in the metabolic activation of carcinogens, changing intracellular physiology in terms of reductive status and oxidative modification of crucial biomolecules (e.g., DNA, lipid proteins) (Samarth et al. 2017). Therefore, it is not surprising the herbal agents and plant extracts use mitigates the radiation damage, and also promotes chemo- and virus- prevention.

In the last 2 years in the COVID-19 pandemic context, herbs and plants are often described as platforms that have been used for the production of reagents and vaccines, particularly through the

clinical testing of infectious diseases and VLP-based vaccines. The possible role of herbs and plants against infectious diseases, for the manufacture of small-molecule drugs, recombinant antivirals, subunit vaccines, engineered viruses, and virus-like particle (VLP) vaccines, therapeutic proteins, antibodies, and diagnostic reagents is profitable and will be usable in medical practice (Roy et al. 2017).

This chapter draws attention to the antioxidant, chemopreventive, radioprotective and anti-virus properties of medicinal plants and their phytoconstituents.

Silybum marianum

The highly appreciated herb, isolated from milk thistle seeds, is Silybum marianum (Silimarin, *S. marianum*) containing a flavonoid complex with active components silibin, silidianin and silicocristine. The beneficial *S. marianum* action is attributed to the most active ingredient silybin/ silibinin. As herb with strong antioxidant properties, directly interacting with cell membrane components, *S. marianum* affects inflammatory responses, cytoprotective effects and cellular regeneration in the body (Madrigal-Santillán et al., 2013; Saeed et al., 2017). Surai et al., 2015 suggested that, the antioxidant mechanism of action is due to the stable free-radical scavenging formations and inhibition of enzyme radicals. The *S. marianum* treatment, in diabetic-burdened patients, leads to superoxide dismutase, glutathione peroxidase levels and total antioxidant capacity regulation (Ebrahimpour et al., 2015). Different studies support, obstruction of metabolic disorders and the stimulatory silymarin role on insulin resistance and hyperlipidemia. *In vitro S. marianum* inhibits lipid peroxidation levels in erythrocyte and hepatocyte cells (Gu et al., 2016; Federico et al., 2017). Bahmani *et al*., 2015 reported that silibinin, modulates lipids membrane oxidation, as well as cell damage in murine hepatocytes. Other evidences of the potent antioxidant *S. marianum* effect and its active compounds has shown that apart from mediating the FXR-signaling, the herb modulates the nuclear transcription factors (Nrf2; NF-kB) (Houghton et al., 2016). Moreover, *S. marianum* promotes anti-inflammatory, anti-fibrosis, anti-proliferative effects, and also protects hepatic tissue increase. The protective *S. marianum* potential against induced hepatotoxicity and against cancers is probably due to its modulating effect on cells in the early stages of the carcinogenic process (Ahmad et al., 2016; Kumar et al., 2017). Choi *et al*., 2017 found that the *S. marianum* and its active substance silibinin act as therapeutic agents for the treatment of salivary gland cancer by targeting the signaling cascade ERK1/ 2-Bim.

In vivo studies demonstrate that by inhibiting myeloid-derived suppressor cells in murine models, silymarin suppressed the lung cancer growth (Liu et al., 2016).

Hepatoprotective effects of *S. marianum* as a cellular natural antioxidant has clinical applications at chronic and alcoholic liver diseases, liver cirrhosis, mushroom poisoning, diabetic patients and viral hepatitis (Masoumi et al., 2016) and prevents of glutathione depletion. Ham et al., 2018 hypothesized that silibibin could be used as dietary supplement treat human placental choriocarcinomas because it inhibits proliferation and induces apoptosis in JAR and JEG3 cells. Recent studies report the silymarin and nano-silymarin role as a cytoprotective agent in normal cells against non-ionizing (UV) or gamma radiation (Adhikari and Arora, 2015; Adhikari and Arora, 2016). Furthermore, the protective *S. marianum* role in chemically induced carcinogenesis and radiation inhibition in colon carcinoma diseases were also established (Hosseinabadi et al., 2019).

Studies from 2020- 2021 show that *S. marianum, W. somnifera, T. cordifolia and A. Barbadensis* extracts exhibited higher binding energetics than the widely used hydroxychloroquine and other repurposed drugs used for COVID–19 treatment (Pandit and Latha, 2020). In two other investigation, substances identified in the human metabolome capable of binding the active site of

the SARS-CoV-2 main protease (Mpro) (Sardanelli et al., 2021); a basis for the design of new silibinin-based antiviral therapeutics or supportive care approaches against the CoV-2 (Nautiyal, et al., 2021). The virus-targeted functions of the flavonolignan silibinin, a potential drug candidate against COVID-19/SARS-CoV, as a direct inhibitor of STAT3—a master checkpoint regulator of inflammatory cytokine signaling and immune response—silibinin might be expected to phenotypically integrate the mechanisms of action of IL-6-targeted monoclonal antibodies and pan-JAK1/2 inhibitors to limit the cytokine storm and T-cell lymphopenia in the clinical setting of severe COVID-19 (Bosch-Barrera et al., 2020).

There is much evidence that silymarin reduces the toxic effects of various mycotoxins. Armanini et all., 2021, feed broiler chickens with food contaminated with mycotoxin. Consumption of feed contaminated with mycotoxin slows weight gain and increases the conversion factor of feed; however, the addition of silymarin prevents these adverse effects. El-Sheshtawy et al., 2021, in the treatment of Peking ducks with food naturally contaminated with aflatoxins, found renal and hepatic damage, evidenced by a number of indicators - serum activities of alanine transaminase and alkaline phosphatase (ALP), glutamyl transfer transfer and albumin, creatinine and uric acid concentrations, oxidant / antioxidant parameters (malondialdehyde [MDA], total antioxidant capacity (TAC), glutathione S-transferase (GST)), and catalase [CAT]). Treatment with silymarin 600 mg / kg food reduces these harmful effects. Jahanian et al., 2017, when administering broiler chickens with a food containing a mixture of aflatoxins, found that the toxins cause reduced average daily food intake (ADFI) and weight gain (ADWG), hence a deterioration in feed conversion ratio (FCR).). The addition of silymarin resulted in a significant increase in ADFI and ADWG and improved FCR values in aflatoxin-infected chickens. According to Rastogi et al., 2001, aflatoxin B (1) induced lipid peroxidation in rat liver and kidney. Significant increases in lipid peroxide levels and concomitant decreases in enzyme antioxidant levels were observed in rats intoxicated with aflatoxin B (1) (2 mg / kg, ip), while drug treatment (picrolium and silymarin) reversed the condition to near normal. levels. Ledur PC et all., 2020 treated in vitro PK-15 cells with ochratoxin A (OTA), fumonisin B1 (FB1) and deoxynivalenol (DON). They concluded that curcumin and silymarin are able to provide cytoprotection against toxicity induced by OTA, FB1 and DON in PK-15 cells. Yu et all., 2017, investigated the hepatotoxicity of ochratoxin A in vitro in primary hepatocytes of chickens. They found that silymarin demonstrated an antitoxic effect against ochratoxin A. Khatoon et al., 2013, investigated the immunotoxic effects of ochratoxin on white leghorn hens. According to the authors, silymarin and vitamin E alone or in combination reduce these harmful effects. Gao X et all., 2018, treated rats with food containing zearalenone. This toxin causes hepatotoxicity and reproductive toxicity. They found that silymarin protected rats from ZEN-induced hepatotoxicity and reproductive toxicity. Sozmen er all., 2018, conducted experiments on the toxicity of fumonisin B1 to the liver of BALB / c mice. The authors found that silymarin improves the toxic damage to the liver caused by this toxin. According to Desplaces et al., 1975, silymarin has hepatoprotective activity in animals (dogs, rabbits, rats, mice) intoxicated with phalloidin. A dose of 15 mg / kg silymarin protects each animal when given 60 minutes before the toxin. When injected 10 minutes after phalloidin, a dose of 100 mg / kg silymarin again provides complete protection. If the time interval between the administration of the toxic substance and the start of treatment increases, the efficacy of silymarin decreases; after 30 minutes its healing effect is insignificant. Histochemical and histoenzymological studies have shown that during intoxication of mice with phalloidin, silymarin inhibits the effect of the toxic substance and regulates hepatocyte function when administered 60 minutes before or 10 minutes

after phalloidin. According to Trost et al., 1978, silibin significantly antagonized the lethal poisoning of mice with alpha-amanitin or phalloidin.

Curcuma longa Linn

The active compound of *C. longa*, (turmeric, ginger, Zingiberaceae family) is the lipophilic polyphenol curcumin (stable at acidic pH). Many authors report that curcumin exhibits antioxidant, anti-carcinogenic and anti-inflammatory affects and is mainly metabolised to turmeric glucuronides, sulphates and etc. in liver (Lal and Gupta, 2016). Similar to vitamins E and C, curcumin exhibits antioxidant activity leading to the neutralization of the oxidative ischemic heart (Labban, 2016) changes. Curcumin treatment induces autophagy, and prevents vasculature endothelial cells from oxidative stress-related cardiovascular diseases (Han et al., 2012). In addition, by exhibiting intracellular antioxidant ability to neutralize oxidative damages, curcumin relieves hepatic oxidative stress in rats with type 1 diabetes (Xie et al., 2017). New findings highlight, that the *C. longa* use with identified high levels of basic polyphenol curcumin, improve insulin-mediated lipid accumulation, directly protect fat cells from oxidative disorders and reduced levels of reactive oxygen species (Septembre-Malaterre etal., 2016). It is known that as strong antioxidant *C. longa* similar to silymarin exhibits hepatoprotective effects. Kim et al., 2014 reported that due to its enhanced hepatoprotective effect, *C. longa* reduced the CCl_4-induced oxidative stress. Simultaneously, leads to increased antioxidant properties by activating the levels of catalase, glutathione S-transferase, glutathione reductase and glutathione peroxidase and reduced glutathione levels. It is proven that low curcumin doses significantly reduce hepatic impairment caused by chronic alcohol intake and a high fat diet.

Probably, antioxidant properties of phenolic groups of curcumin protect cells from lipid peroxidants and modulate the activity of alcohol-metabolizing enzymes and induced hepatotoxicity (Lee et al., 2013). Several studies underline attenuating effects and the antioxidant role of curcumin, the proliferation of human lymphocytes and the production of inflammatory mediators (Ghandadi and Sahebkar, 2017). Similar curcumin activity was also observed in the propoxur-induced oxidative DNA damage in human peripheral blood mononuclear cells (Ahmed et al., 2017). The powerful antidote curcumin properties are also reported and the ability to neutralize lead-induced genotoxicity, by balancing activity of antioxidant protective system in human peripheral blood lymphocytes (Nariya et al., 2017).

C. longa, with curcumin as main ingredient, has protective effects against radiation-induced damage, reduces levels of superoxide anion radicals and reduces DNA damage and oxidative stress (Cervelli et al., 2017; Rao et al., 2013). Rao et al., 2013, disclose that the *C. longa* use in the form of mouthwash, had delayed and statistically significantly reduced the levels of radiation-induced oral mucositis, observed in patients undergoing head and neck cancer treatment. Many researchers comment the antioxidant action of herbs and medicinal plants combinations, their high efficacy and lack of residual toxicity in preventing damage from X-ray radiation exposure. In another investigation (Jaikumar et al., 2016), authors supposed that protective *C. longa* effect extract against γ-radiation is responsible for modulating the levels of microelements, antioxidant enzymes and inflammatory cytokines. In addition, *in vitro* protective effect of new RIDROS natural mixture, containing *C. longa*, significantly reduces oxidative stress and DNA double-strand breaks and fully absorbed low doses of X-rays (0.25 Gy) in human umbilical vein endothelial cells (Jaikumar et al., 2016). Also, *C.longa* extracts stimulate glutathione transferase and prevent cell proliferation possessed breast cancer activity (Jasmine R, 2016).

Haberlea rhodopensis (Friv.)

Typical for Balkan region *H. rhodopensis* is a perennial medicinal plant, (Gesneriaceae family) rich in luteolin, hexeridine, synapic and ferulic acid, caffeifloylethyanoid glycoside miconoside, characterized by the strong antioxidant properties of its extracts (Mihaylova et al., 2013). It is proven that the higher phenolic content in 70% ethanol extracts of *H. rhodopensis* directly correlates with high antioxidant activity (Mihaylova et al., 2013) and increased free-radical inhibition. Georgieva *et al.*, 2013 notes that *H. rhodopensis* as natural product plays a modulatory role *in vitro* against cellular damage, induced by γ-irradiation and its high antioxidant capacity increases the activity of cellular SOD and CAT. In addition, *H. rhodopensis* extracts after metabolic profiling not reported any cytotoxic activity, have anti-radical properties and are useful as phytotherapeutic agents (Todorova, Atanasov, 2016). Kostadinova et al., 2016 reported that the extracts of *H. rhodopensis* have a beneficial effect on mitochondrial activity, the integrity of cell membranes in human (HaCaT) keratinocytes, by reducing inflammatory processes and reducing ROS. Drought-induced oxidative damages increase the content of polyphenols and two types of glycosides - phenylethanoids and xispidulin 8-C-glucosides in the structure of *H. rhodopensis.* Probably, this plays a protective role on the medicinal plant, helps overcome oxidative changes by reprogramming and redirecting resources to cell protection and significantly increased antioxidant capacity (Mihaylova et al., 2015; Georgieva et al., 2017). Besides ethanol and methanol extracts of *H. rhodopensis* exhibit an antioxidant effect by reducing H_2O_2-induced toxicity in both normal and malignant cell lines (Djilianov et al., 2016). The radioprotective and immunomodulatory properties of the *H. rhodopensis* extract were evaluated in rabbits after 2Gy irradiation (Dobreva et al., 2015). The phenolic compounds isolated from H. rhodopensis demonstrate cytoprotective properties and contribute the inhibition of lipid peroxidation in rat hepatocytes (Kondeva-Burdina et al., 2013).

Conclusion

Plant antioxidants dose protects against oxidative disorders or completely neutralized chemo- or virus-induced oxidative stress. Different studies provide information about efficacy, chemopreventive plant-antioxidants, and microbial species as therapeutic agents against drug-induced toxicity and there were widely used in traditional medicine.

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References

1. Adhikari, M.; Arora R. Nano-silymarin provides protection against γ-radiation-induced oxidative stress in cultured human embryonic kidney cells. Mutation Res/Genetic Toxicol Environm. Mutagenesis., 2015, 792,1-11.
2. Adhikari, M.; Arora, R. The flavonolignan-silymarin protects enzymatic, hematological, and immune system against γ-radiation-induced toxicity. *Environmental Toxicol*., 2016, 31(6), 641-654.
3. Ahmad, I.; et al. Biochemical and molecular mechanisms of N-acetyl cysteine and silymarin-mediated protection against maneb- and paraquat-induced hepatotoxicity in rats. *Chem. Biol. Interact*., 2013, 201(1-3), 9–18.

4. Ahmed, T.; Goel, V.; Banerjee, B.D. Propoxur-induced oxidative DNA damage in human peripheral blood mononuclear cells: protective effects of curcumin and α-tocopherol. *Drug and chemical toxicol*., 2017, 1-7. On-line https://doi.org/10.1080/01480545.2017.1321010
5. Armanini EH, Boiago MM, Cécere BGO, Oliveira PV, Teixeira CJS, Strapazzon JV, Bottari NB, Silva AD, Fracasso M, Vendruscolo RG, Wagner R, Gloria EMD, Horn VW, Mendes RE, Baldissera MD, Vedovatto M, Da Silva AS. Protective effects of silymarin in broiler feed contaminated by mycotoxins: growth performance, meat antioxidant status, and fatty acid profiles. Trop Anim Health Prod. 2021 Aug 19;53(4):442.
6. Bahmani, M.; Shirzad, H.; Rafieian, S.; Rafieian-Kopaei, M. *Silybum marianum*: beyond hepatoprotection. *J. Evid. Based Complementary Altern. Med.*, 2015, 20, 292–301.
7. Bosch-Barrera J, Martin-Castillo B, Buxó M, Brunet J, Encinar JA, Menendez JA. Silibinin and SARS-CoV-2: dual targeting of host cytokine storm and virus replication machinery for clinical management of COVID-19 patients. Journal of clinical medicine. 2020; 9(6):1770
8. Cervelli, T.; Panetta, D.; Navarra, T.; Gadhiri, S.; Salvadori, P.; Galli, A.; Caramella, D.; Basta, G.; Picano, E.; Del Turco, S. A new natural antioxidant mixture protects against oxidative and DNA damage in endothelial cell exposed to low-dose irradiation. *Oxidative Med Cell. Longevity.*, 2017, Article ID 9085947, 7.
9. Choi, E.S.; Oh, S.; Jang, B.; Yu, H.J.; Shin, J.A.; Cho, N.P.; Yang, I.H.; Won, D.H.; Kwon, H.J.; Hong, S.D.; Cho, S.D. Silymarin and its active component silibinin act as novel therapeutic alternatives for salivary gland cancer by targeting the ERK1/2-Bim signaling cascade. *Cellular Oncol.*, 2017, 40(3), 235-246.
10. Cohen, P.A.; Ernst, E. Safety of herbal supplements: A guide for cardiologists. *Cardiovasc Ther.*, 2010, 28, 246–253.
11. Desplaces A, Choppin J, Vogel G, Trost W. The effects of silymarin on experimental phalloidine poisoning. Arzneimittelforschung. 1975 Jan;25(1):89-96
12. Djilianov, D.L.; Moyankova, D. P.; Mladenov, P.V. The Mediterranean: a cradle of the resurrection plants in Europe. *Phytologia Balcanica*., 2016, 22(2), 141–147.
13. Dobreva, Z.G.; Popov, B.N.; Georgieva, S.Y.; Stanilova, S.A. Immunostimulatory activities of Haberlea rhodopensis leaf extract on the specific antibody response: protective effects against γ-radiation-induced immunosuppression. *Food and Agricul Immunol*., 2015, 26(3), 381-393.
14. Ebrahimpour, Koujan. S.; Gargari, B.P.; Mobasseri, M.; Valizadeh, H.; Asghari-Jafarabadi, M. *Effects of Silybum marianum (l.) gaertn.*(silymarin) extract supplementation on antioxidant status and hs-CRP in patients with type 2 diabetes mellitus: A randomized, triple-blind, placebo-controlled clinical trial. *Phytomed*.; 2015, 22(2), 290-296.
15. El-Sheshtawy SM, El-Zoghby AF, Shawky NA, Samak DH. Aflatoxicosis in Pekin duckling and the effects of treatments with lycopene and silymarin. Vet World. 2021 Mar;14(3):788-793
16. Federico A, Dallio M, Loguercio C. Silymarin/Silybin and Chronic Liver Disease: A Marriage of Many Years. *Molecules* 2017, *22*(2), 191
17. Gao X, Xiao ZH, Liu M, Zhang NY, Khalil MM, Gu CQ, Qi DS, Sun LH. Dietary Silymarin Supplementation Alleviates Zearalenone-Induced Hepatotoxicity and Reproductive Toxicity in Rats. J Nutr. 2018 Aug 1;148(8):1209-1216
18. Georgieva, K.; Dagnon, S.; Gesheva, E.; Bojilov, D.; Mihailova, G.; Doncheva, S. Antioxidant defense during desiccation of the resurrection plant Haberlea rhodopensis. *Plant Physiol Biochem*., 2017, 114, 51-59.

19. Georgieva, S.; Popov, B.; Bonev, G. Radioprotective effect of Haberlea rhodopensis (Friv.) leaf extract on gamma-radiation-induced DNA damage, lipid peroxidation and antioxidant levels in rabbit blood. *Indian J Exp Biol.*, 2013, 51, 29-36.
20. Ghandadi, M.; Sahebkar, A. Curcumin: An Effective Inhibitor of Interleukin-6. *Current Pharmaceut. Design.*, 2017, 23(6), 921-931.
21. Gu, M.; Zhao, P.; Huang, J.; Zhao, Y.; Wang, Y.; Li, Y.; Fan, S.; Ma, Y.M.; Tong, Q; Yang, L; Ji, G; Huang, C. Silymarin ameliorates metabolic dysfunction associated with diet-induced obesity via activation of farnesyl x receptor. *Front Pharmacol*., 2016, 7:345.
22. Ham, J.; Lim, W.; Bazer, F.W.; Son, G. Silibinin stimluates apoptosis by inducing generation of ROS and ER stress in human choriocarcinoma cells. *J Cell Physiol*., 2018, 233(2), 1638–1649.
23. Han, J.; Pan, X-Y.; Xu, Y.; Xiao, Y.; An, Y.; Tie, L.; Pan, Y.; Li, X-J. Curcumin induces autophagy to protect vascular endothelial cell survival from oxidative stress damage. *Autophagy*, 2012, 8(5), 812-825.
24. Hosseinabadi T, Lorigooini Z, Tabarzad M, Salehi B, Rodrigues CF, Martins N, Sharifi-Rad J. Silymarin antiproliferative and apoptotic effects: insights into its clinical impact in various types of cancer. Phytotherapy Research. 2019;33(11):2849-61.
25. Houghton, C.A.; Fassett, R.G.; Coombes, J.S. Sulforaphane and other nutrigenomic Nrf2 activators: Can the clinician's expectation be matched by the reality? *Oxid Med Cell Longev*., 2016, 2016, 7857186.
26. Jahanian E, Mahdavi AH, Asgary S, Jahanian R. Effects of dietary inclusion of silymarin on performance, intestinal morphology and ileal bacterial count in aflatoxin-challenged broiler chicks. J Anim Physiol Anim Nutr (Berl). 2017 Oct;101(5):e43-e54
27. Jaikumar B, Jasmine R. A Review on a few medicinal plants possessing anticancer activity against human breast cancer. *Internat J PharmTech Res*., 2016. 9(3), 333-365.
28. Khatoon A, Zargham Khan M, Khan A, Saleemi MK, Javed I. Amelioration of Ochratoxin A-induced immunotoxic effects by silymarin and Vitamin E in White Leghorn cockerels. J Immunotoxicol. 2013 Jan-Mar;10(1):25-31
29. Kim, Y.; You, Y.; Yoon, H.G.; Lee, Y.H.; Kim, K.; Lee, J.; Kim, M.S.; Kim, J.C.; Jun, W. Hepatoprotective effects of fermented Curcuma longa L. on carbon tetrachloride-induced oxidative stress in rats. *Food Chem*., 2014, 151, 148-153.
30. Kondeva-Burdina, M.; Zheleva-Dimitrova, D.; Nedialkov, P.; Girreser, U.; Mitcheva, M. Cytoprotective and antioxidant effects of phenolic compounds from Haberlea rhodopensis Friv. (Gesneriaceae). *Pharmacognosy Mag.*, 2013, 9(36), 294-301.
31. Kostadinova, A.; Doumanov, J.; Moyankova, D.; Ivanov, S.; Mladenova, K.; Djilianov, D.; Topouzova-Hristova, T. Haberlea Rhodopensis extracts affect cell periphery of keratinocytes. *Comptes rendus de l'Acad´emie bulgare des Sci*., 2016, 69 (4), 439-448.
32. Kumar, T.; Larokar, K.Y.L.; Iye, S.K.; Kumar, A.; Tripathi, D.K. Phytochemistry and Pharmacological Activities of Silybum marianum: A Review. Intern. J Pharmac. Phytopharmacol. Res., 2017, 1(3), 2011.
33. Labban, L. Medicinal and pharmacological properties of Turmeric (Curcuma longa): A review. *Int J Pharm Biomed Sci.*, 2016, 5(1), 17-23.
34. Lal, M.; Gupta, D. Studies on radiation sensitization efficacy by silymarin in colon carcinoma cells. *Discoveries.*, 2016, 4(1): e56 DOI: 10.15190/d.2016.3.
35. Ledur PC, Santurio JM. Cytoprotective effects of curcumin and silymarin on PK-15 cells exposed to ochratoxin A, fumonisin B_1 and deoxynivalenol. Toxicon. 2020 Oct 15;185:97-103

36. Lee, H.I.; McGregor, R.A.; Choi, M.S.; Seo, K.I.; Jung, U.J.; Yeo, J.; Kim, M.J.; Lee, M.K. Low doses of curcumin protect alcohol-induced liver damage by modulation of the alcohol metabolic pathway, CYP2E1 and AMPK. *Life Sci*., 2013, 93(18–19), 693-699.
37. Liu,W.; .; ZhuaX. Silymarin suppressed lung cancer growth in mice via inhibiting myeloid-derived suppressor cells. *Biomed & Pharmacotherapy.*, 2016, 81, 460-467.
38. Lobato M, Huang X, Alvarez D, He W, Baysal C, Zhu C, Armario-Najera V, Blanco Perera A, Cerda P, Saba-Mayoral A, Sobrino-Mengual G. Contributions of the international plant science community to the fight against infectious diseases in humans-part 1: epidemic and pandemic diseases, including HIV/AIDS and coronaviruses. Plant Biotechnology Journal, 2021, 19, 1901-1920).
39. Madrigal-Santillán, E.; Madrigal-Bujaidar, E.; Cruz-Jaime S.; Valadez-Vega, M.C.; Sumaya-Martínez, M.T.; Pérez-Ávila, K.G. The chemoprevention of chronic degenerative disease through dietary antioxidants: progress, promise and evidences, in Oxidative Stress and Chronic Degenerative Diseases-a Role for Antioxidants, ed Morales-González J. A., editor, (*Rijeka: Croatia In Tech*), 2013, 155–185.
40. Masoumi, H.; Anjamshoa, M.; Mohammadi, M.; Fallahi, S.; Rostamzadeh, A. Clinical and pharmacological applications of silymarin components at cellular and molecular level: A review. Research J. Medical Sci., 2016, 10(3), 102-107.
41. Mihaylova, D.; Bahchevanska, S.; Toneva, V. Examination Of The Antioxidant Activity Of Haberlea Rhodopensis Leaf Extracts And Their Phenolic Constituents. *J Food Biochem.*, 2013, 37(3), 255–261.
42. Mihaylova, D.; Lante, A.; Krastanov, A. Total phenolic content, antioxidant and antimicrobial activity of Haberlea rhodopensis extracts obtained by pressurized liquid extraction. *Acta Alimentaria*., 2015, 44(3), 326–332.
43. Nariya, A.; Pathan, A.; Shah, N.; Chettiar, S.; Alpesh, P.; Jignasha, D.; Divya C,.; Mandava, R.; Devendrasinh, J. Ameliorative effects of curcumin against lead induced toxicity in human peripheral blood lymphocytes culture. *Drug and Chem Toxicol*., 2017, 41(1), 1-8.
44. Nautiyal, Bhagwan, Amit Kumar, and Jitender K. Malik. "SARS-CoV-2: Silibinin Prospects in Antiviral Drug Development., 2021.
45. Pandit, A.; Sachdeva, T.; Bafna, P. Drug-induced hepatotoxicity: a review. *J. Appl. Pharm. Sci*., 2012, 02, 233–243.
46. Pandit, Mansi, and N. Latha. "In silico studies reveal potential antiviral activity of phytochemicals from medicinal plants for the treatment of COVID-19 infection, 2020.
47. Rao, S.; Dinkar, C.; Vaishnav, L.K.; Rao, P.; Rai, M.P.; Fayad, R.; Shrinath, M.B. The Indian Spice Turmeric Delays and Mitigates Radiation-Induced Oral Mucositis in Patients Undergoing Treatment for Head and Neck Cancer. *Integrative Cancer Therapies*., 2013, 13(3), 201-210.
48. Rastogi R, Srivastava AK, Rastogi AK. Long term effect of aflatoxin B(1) on lipid peroxidation in rat liver and kidney: effect of picroliv and silymarin. Phytother Res. 2001 Jun;15(4):307-10.
49. Roy, A.; Bharadvaja, N. Medicinal Plants in the Management of Cancer: A Review. *Intern. J Complement. & Alternative Med.*, 2017, 9(2), 00291.
50. Saad, B.; Zaid, H.; Shanak, S.; Kadan, S. Introduction to Medicinal Plant Safety and Efficacy. Anti-diabetes and Anti-obesity Medicinal Plants and Phytochemicals. *Springer, Cham.*, 2017, 21-55.

51. Saeed, M.; Babazadeh, D.; Arif, M.; Arain, M.A. Silymarin: a potent hepatoprotective agent in poultry industry. *World's Poultry Sci J*., 2017, 73(3), 483-492.
52. Samarth, R.M.; Samarth, M.; Matsumoto, Y. Medicinally important aromatic plants with radioprotective activity. *Future Sci. OA*., 2017, 3(4), FSO247.
53. Sardanelli AM, Isgrò C, Palese LL. SARS-CoV-2 Main Protease Active Site Ligands in the Human Metabolome. Molecules. 2021;26(5):1409.
54. Septembre-Malaterre, A.; Le Sage, F.L.; Hatia, S.; Catan, A.; Janci, L.; Gonthier, M.P. Curcuma longa polyphenols improve insulin-mediated lipid accumulation and attenuate proinflammatory response of 3T3-L1 adipose cells during oxidative stress through regulation of key adipokines and antioxidant enzymes. *Biofactors*., 2016, 42(4), 418–430.
55. Singh, D.; Cho, W.C.; Upadhyay, G. Drug-Induced Liver Toxicity and Prevention by Herbal Antioxidants: An Overview. *Frontiers in Physiol*., 2015, 69, 363.
56. Sozmen M, Devrim AK, Tunca R, Bayezit M, Dag S, Essiz D. Protective effects of silymarin on fumonisin B_1-induced hepatotoxicity in mice. J Vet Sci. 2014;15(1):51-60
57. Surai, P.F. Silymarin as a natural antioxidant: an overview of the current evidence and perspectives. *Antioxidants*, 2015, 4, 204-247.
58. Todorova, R.; Atanasov, A.T. Haberlea rhodopensis: pharmaceutical and medical potential as a food additive. Natural Product Research. *Formerly Nat Prod Letters*., 2016, 30(5), 507-529.
59. Trost W, Halbach G. Anti-phalloidine and anti-alpha-amanitine action of silybin in comparison with compounds similar to structural parts of silybin. Experientia. 1978 Aug 15;34(8):1051-2.
60. Vallejo, M.J.; Salazar, L.; and Grijalva, M. Oxidative Stress Modulation and ROS-Mediated Toxicity in Cancer: A Review on In Vitro Models for Plant-Derived Compounds. *Oxid Med and Cell Longevity*, 2017, Article ID 4586068, doi:10.1155/2017/45860682017.
61. Watson, R.R.; Preedy, V.R. (Eds). Botanical Medicine in Clinical Practice. *CAB International Publishing, UK*, 2008, pp. 915.
62. Xie, Z.; Wu, B.; Shen, G.; Li, X.; Wu, Q. Curcumin alleviates liver oxidative stress in type 1 diabetic rats. *Molecul. Med. Reports*., 2017, 17, 103-108.
63. Yu Z, Wu F, Tian J, Guo X, An R. Protective effects of compound ammonium glycyrrhizin, L-arginine, silymarin and glucurolactone against liver damage induced by ochratoxin A in primary chicken hepatocytes. Mol Med Rep. 2018 Sep;18(3):2551-2560
64. Zgheib, N.K.; Branch, R.A. Drug metabolism and liver disease: a drug–gene–environment interaction. *Drug Metabolism Rev*., 2017, 49, 35-55.