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Title

MULTIFUNCTIONAL PENTACYCLIC TRITERPENOIDS AS ADJUVANTS IN CANCER CHEMOTHERAPY: A REVIEW

Running title

PROTECTIVE ADJUVANTS IN CANCER TREATMENT

Author names and affiliations

Sarika M. Kamble[1], Sameer Goyal[1] and Chandragouda R. Patil[1]

[1] Drug Discovery Laboratory, Department of Pharmacology, R. C. Patel Institute of Pharmaceutical Education and Research, Karvand Naka, Shirpur, Dist. Dhule, Maharashtra, India 425405

Corresponding author.

Dr. Chandragouda R. Patil,

HOD and Professor,

Drug Discovery Laboratory,

Department of Pharmacology,

R. C. Patel Institute of Pharmaceutical Education & Research Center, Karvand Naka, Shirpur, 425405, Dist. Dhule, Maharashtra, India. 425405

Telephones: +919850115505, +912563255189, fax: +912563251808

Email: pchandragouda@yahoo.com

Abstract

Chemotherapeutic agents are a mainstay in the treatment of cancer. However, non-selectivity of cytotoxic anticancer agents results in multi-organ toxicities. Cancer chemotherapy is often associated with toxicities which can be expensive to manage and may affect patient's quality life. Very few organ protective agents like amifostine are proved as adjuvants to cancer chemotherapy. Amifostine protects against a wide range of chemo and radiotherapy related toxicities and reduces costs of supportive care. Multifunctional natural compounds like pentacyclic triterpenoids and their semisynthetic derivatives possess organ protective activities against drug induced toxicities. Triterpenoids interact with biomolecules involved in the cytotoxicity of chemotherapeutic agents. They also sensitize the cancer cells for cytotoxic effect of chemotherapy. Further, pentacyclic triterpenoids themselves possess anticancer activity. The efficacy of pentacyclic triterpenoids as organotropic, anticancer and chemo sensitizers may prove these agents as an adjuvant to cancer chemotherapy.

Current review focuses on systematic studies of multifunctional role of pentacyclic triterpenoids and their derivatives in chemotherapy. Interactions of pentacyclic triterpenoids with molecular targets of like nuclear factor erythroid-derived like 2 (NrF2), nuclear factor kappa B (NFκ-B), protein kinase C (PKC), free radical scavenging, and cell longevity pathways that contribute to cytoprotective, anticancer, chemosensitizer and chemopreventive effects have been emphasized. Therapeutic utility of pentacyclic triterpenoids as multifunctional adjuvants to the cancer chemotherapy is highlighted.

Keywords: Adjuvant; Cancer chemotherapy; NrF2; NFκ-B; Pentacyclic triterpenoids; PKC

Main text

1. Introduction

Chemotherapeutic agents used in the treatment of cancer exert dose dependent severe multiorgan toxicities [1-3]. An approach of targeted treatment with monoclonal antibodies is an emerging trend in cancer therapy that promises reduced organ toxicities. However, these targeted therapies have their own immune related side effect, and have other disadvantages including high cost [4, 5]. Further, novel site specific antibody-drug conjugate based treatment is under clinical investigation [6]. Even in this mode of treatment is marred with other imitations in terms of site specific delivery of chemotherapeutic agent and formulation related problems. Hence, use of traditional cytotoxic drugs is continues to be a preferred mode for the treatment of cancer.

To minimize the multiorgan toxicities of cancer chemotherapy, organ protective adjuvants are also prescribed. Organ protectants are under clinical investigation and few drugs including amifostine are FDA adjuvants to cancer chemotherapy. Drugs like amifostine [7], alpha-lipoic acid [8], dexerazoxon, mesna, leucovorin, GM-CSF, recombinant erythropoietin, thrombopoietin [9], imidazenil [10] and KR-22335 [11] are used as organ protective adjuvants to the cancer chemotherapy. Clinical and preclinical studies are having projected selenium, with and without the vitamins as dietary adjuvants [12, 13]; moreover many natural bioactive agents are also able to restore the microstructure from hazardous chemical [14]. However, shortcomings of currently available adjuvants in terms of pharmacoeconomics, short term efficacy, and innate adverse effects limit their use. It is expected that adjuvants should not interfere with the cytotoxic effect of chemotherapy against cancer cells. To suffice such demands there is need ideal organ protective agents that do not interfere with expected effects of chemotherapy without producing cumulative or irreversible toxicity. Further, such agent should provide effective long term protection, should be easily administrable and should have acceptable shelf life [15]. These agents selectively protect the normal body cells from toxicities of chemotherapy with or without antagonizing the anticancer efficacy of chemotherapy. The currently used organ protectants are not devoid of innate toxicities. Thus, there is a need of an ideal, cost-effective, safe adjuvant to cancer chemotherapy that can protect normal body cells from cytotoxic actions and sensitize the cancer cell to chemotherapeutic agent. Apart from synthetic agent, naturally occurring agent may prove to be better adjuvants to cancer therapy [16, 17].

Pentacyclic triterpenoids, widely distributed in the plant kingdom, have been extensively reported to possess protective effects against drug induced organ toxicities including those of chemotherapeutic agents (Table

1). These agents exert a plethora of effects by interacting with multiple biomolecules. Their easy availability and routine consumption across all the world populations point towards their safely. Hence, pentacyclic triterpenoids and their semisynthetic and/synthetic derivatives can be projected as organ protective adjuvants to chemotherapy [39, 40].

2. Chemotherapy, chemoprevention and adjuvant to chemotherapy:

The success of chemotherapy depends upon its administration at effective dose levels in an inflexible and programmed manner. However, such inflexible dosing schedules can be rarely followed in cancer therapy due to dose-limiting toxicities and related perversions in the recipient's quality of life. Thus, the cytotoxic efficacy of the chemotherapeutic agents can't be exploited. There is a need of organ protective adjuvants to continue the chemotherapy at effective dose levels along with either protecting the normal body cells against chemotherapy induced toxicities or sensitizing the cancer cells to cytotoxic effects of chemotherapy [39, 41]. In addition to protection of normal cells from cytotoxicity, an approach of sensitizing the cancer cells to chemotherapy can help in reducing the dose of chemotherapeutic agents. The successful outcome of cancer chemotherapy depends on additional treatment with other agents given concurrently or after the primary treatment that lowers the untoward multi-organ damage inflicted by the chemotherapeutic agents. Obviously, such additional treatment is expected to boost the anticancer activity of the chemotherapeutic agents or at least should not antagonize their actions. The ideal outcomes of the adjuvant therapy include protection of noncancerous cells leading to maintenance of normal functioning of vital organs. Though, the use of targeted drugs is and emerging trend in cancer therapy, it is not devoid of the associated toxicities and hence, use of cytotoxic drugs for cancer treatment is universally recommended [42]. Obviously co-administration of organ protective adjuvant therapy is warranted and there is need of adjuvants which can synergistically contribute to the effects of chemotherapy.

3. Multifunctionality of pentacyclic triterpenoids as adjuvants to chemotherapy:

Pentacyclic triterpenoids are widely distributed in plant kingdom and their semisynthetic derivatives and synthetic analogous possess molecular globularity which enables them to interact with multiple biological targets. Pentacyclic triterpenes contain 30-carbon skeleton having six-membered rings (ursanes and lanostanes) and five-membered ring (lupanes and hopanes). Pentacylic triterpenoids are secondary metabolites widespread in fruit peels, leaves and stem bark especially in mediterranean plant species with percentage availability of 0.1 to 3% [43, 44].

Triterpenoids possess organotropic nature and accumulate in multiple vital organs. The organ protective efficacy of pentacyclic triterpenoids has been substantiated through preclinical evaluations. The protective efficacy of pentacyclic triterpenoids through organotrophism and interactions with different molecular targets is summarized in Figure 1 and Table 2.

Triterpenoids are neither conservative cytotoxic agent, nor are they monotargeted drugs that inimitably target the single pathway. Some synthetic triterpenoids possess multipronged effects on cancer, inflammation, oxidative stress, proliferation of cancer cells, apoptosis and cytoprotection [115].

3.1 Molecular pathways underlying protective effects pentacyclic triterpnoids:

3.1.1. Upregulation of NrF2 pathway for cytoprotection

NrF2 is also called as a cap'n'collar bZIP transcription factor. It controls the expression of several enzymes that protect against oxidative stress [116]. NrF2 consists of six highly conservative domains Neh1 to Neh6; the Neh2 is a N-terminal domain that takes part in redox dependent regulation of protein stability due to its attachment to Kelch-like ECH-associated binding protein (Keap-1) and conjugation with ubiquitin [117]. Once NrF2 protein enters and stabilizes inside the nucleus, it gets dimerized with Maf proteins and transactivates several antioxidant enzymes [118]. NrF2 is a cell signaling transcriptional factor that generates cytoprotective phase II antioxidant enzymes such as GST, SOD, CAT, NQO1 and HO-1[119, 120]. These enzymes are responsible for detoxifying harmful materials in the body. Phase II antioxidant enzymes are responsible for the organotropic and chemoprotective effect from anticancer drug like cisplatin [120].

A study by Yap *et al*. concludes that maslinic acid and oleanolic acid increase the NrF2 expression and nuclear translocation up to 172 % and 124 % respectively. This finding was validated through estimations of phase-II antioxidant like HO-1 and NQO1 in HepG2 cell lines. Thus, the organ protective efficacy of maslinic acid and oleanolic acid is credited to their effects on NrF2 pathway [60]. Another triterpenoid, celastrol, increases expression of HO-1 via NrF2 translocation in the HaCat cell lines. Through NrF2 driven HO-1 expression celastrol exerts anti-inflammatory effect also reverts TNF-α and interferon-γ-induced ICAM expression in karatinocytes [70]. A study by Reisman *et al*. establishes that oleanolic acid, at a dose of 90 mg/kg/day administered to mice for three days, increases NrF2 translocation driven expression of HO-1 and NQO1 phase-II enzymes in the acetaminophen induced hepatotoxicity model [77]. Liby *et al*. denote that synthetic derivatives of oleanolic acid like CDDO and CDDO-

imidazolide are strong inducers of NrF2 pathway and should be investigated for chemopreventive or chemotherapeutic agent. In their study, they used $NrF2^{++}$ and $NrF2^{--}$ mice as well as U937 and THP-1 cell lines. The northern blot analysis of vital organs and estimations of HO-1 induction substantiate that triterpenoids may also inhibit AKT and PKC pathway [121]. Synthetic derivative of oleanolic acid, CDDO-methyl amide induce translocation of NrF2. To prove this, NrF2 knockout mice to verify the translocation factor via immunohistochemisty and sterologic analysis in the 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridin (MPTP) induced parkinsonism in fibrobast cells, which shows the increase levels of GSH, HO-1 and NQO1 and revert the neurotoxicity [122]. Recently, patents have been filed for synthetic derivative of triterpenoids for their NrF2 translocation driven organ protective effects in various diseases associated with increased oxidative stress [123].

Interaction of pentacyclic triterpenoids with Keap-1 leads to accumulation of NrF2 in the cell nucleus and induces antioxidant response element (ARE)-driven gene expression which is the most important regulator of cell defense against chemical/oxidative stress [41, 124]. Chemotherapeutic agents like doxorubicin affect the functioning of vital organs through oxidative stress. Hence, it can be postulated that pentacyclic triterpenoids are agents which induce nuclear translocation of NrF2 [92, 121-123, 125] and protect the vital organs without inhibiting the cytotoxic efficacy of chemotherapeutic agent in cancer cells.

3.1.2. NFκ-B inhibition for cytoprotection

Activation of NFκ-B pathway is a common process in the pathogenesis of multiple malignancies including leukemias, lymphomas, and solid tumors of breast, ovary, prostate, and colon [126]. Down regulation of NFκ-B pathway by natural product can be a rational mode to curb the cancer growth [127]. NFκ-B is implicated in cytoprotection from undergo apoptosis in response to DNA damage exercise by chemotherapy. The NFκ-B pathway is regulated by diverse signal transduction cascades that include the activities of IKβ kinases, IKKα and IKKβ. The degradation of IKβ cause the translocation of NFκ-B from the cytoplasm to nucleus which further activate cellular genes expression. Down regulation of the NFκ-B pathway increases the sensitivity of cells to apoptosis [128, 129]. Agents inhibiting the NFκ-B pathway decrease the expression of VCAM-1 and ICAM-1 in endothelial cells [61, 129, 130]. Thus, an approach of inhibiting the NFκ-B pathway through concurrent administration of pentacyclic triterpenoids may increase the efficacy of cancer chemotherapy with reduced cytotoxicity [131].

Semisynthetic acyl derivatives of boswellic acid are reported to inhibit NFκ-B pathway in the different cancer cell lines. The systematic evaluation of such compounds may prove new era of anticancer agents [132].

Arjunolic acid was also proven its NFκ-B pathway modulation in the streptozotocin (STZ)-induced type 1 diabetes. The study also stated that pentacyclic triterpenoids have free radical scavenging potential and modulate that MAPK and NFκ-B pathways. Arjunolic acid revert the cellular hepato toxicity in diabetes [56]. Maslinic acid, a naturally occurring pentacyclic triterpenoid, modulates NFκ-B translocation in the Raji cell line and also inhibits COX-2 expression in them. The ability of maslinic acid to modulate NFκ-B and COX-2 indicates probable antitumor and anti-inflammatory efficacy of maslinic acid [58]. Similarly, asiatic acid inhibits nuclear translocation of NFκ-B through possible degradation of IKKβ in lipopolysccharide (LPS)-stimulated RAW cell line. This report emphasizes that asiatic acid also modulates the activities of p38, COX-2 and TOLL receptor making it an ideal agent in treatment of inflammation and cancer [88]. Another pentacyclic triterpenoid, madecassic acid inhibits NFκ-B pathway and exerts inhibitory effect on iNOS, COX-2, IL-1,-6 and TNF-α expression in LPS-stimulated RAW cells. The inhibitory concentration ranges between 50 to 150 μM/mL indicating potential anti-inflammatory and anticancer activity of the madecassic acid [65]. Another study shows that the pretreatment with madecassoside revert LPS-induced cytotoxicity in the neonatal rat cardiomyocytes [63]. Another abundantly available triterpenoids, ursolic acid, inhibits NFκ-B translocation and suppresses the COX-2, MMP-9 and TNF [107]. Similar effects are reported for lupeol and it has been claimed as a potential agent in treatment of skin carcinogenesis [133].

NFκ-B activation is involved in the progression of a tumor as well as in the vital organ damage by the chemotherapeutic agents. There is a homeostatic balance between NFκ-B and NrF2 expression in the cellular microenvironment. Inhibition of NFκ-B increases NrF2 translocation and provides cytoprotection against oxidative stress [134]. Pentacyclic triterpenoids are well reported for inhibiting the NFκ-B pathway [48, 135] and hence can be projected to be a component of the arsenal against cancer as an anticancer as well as an organ protective agent.

3.1.3. Free radical scavenging activity:

The toxic electrophiles generated from chemotherapeutic agents and their metabolites exert oxidative stress [136]. Apart from this, the effects of chemotherapy generate free radicals like hydroxyl ion ($OH^{\cdot}$), nitric oxide ($NO^{\cdot}$), nitrites ($NO_2^{\cdot}$), peroxyl radicals ($RO_2^{\cdot}$), alkoxy radicals ($RO^{\cdot}$), carbonate radicals ($CO_3^{\cdot-}$) and superoxide anion ($O_2^{\cdot-}$) [137]. For example, the metabolites of doxorubicin namely semiquinone and quinone radicals are more reactive than doxorubicin itself and hence exert severe cytotoxicity [138]. They impede with the nucleophilic macromolecules of DNA, RNA, proteins and amino acids; these reactions in turn results in to lipid peroxidation, DNA damage, cytoskeletal damage, protein oxidation and multi-organ toxicity [139-141]. Pentacyclic triterpenoids

provide protection against oxidative stress through multiple modes like scavenging of free radicals, donating hydrogen ions to free radicals, depleting oxygen and directly binding and inactivating toxic free radicals. Such effects of pentacyclic triterpenoids inhibit DNA damage and support the process of DNA repair [7].

Betulinic acid reduces oxidative stress and augments of antioxidant enzyme level like SOD, LDH, GST and also decreases lipid peroxidation in 7,12-dimethylbenzanthracene-induced carcinogenesis in mice [142]. It has potential to revert the oxidative and nitrosative stress [49]. Other widely studies and easily extractable naturally occurring pentacyclic triterpenoids like oleanolic acid and its derivatives are reported to exert cytoprotective actions against hydrochloric acid and ethanol induced gastric lesions in mice. They also exert cytoprotection against sodium taurocholate-induced cell damage in AGS cells. This study substantiates that, the effect of oleanolic acid is better than that of sucralfate. These protective effects are associated with an increase prostaglandins, SOD and GSH levels [143]. Another triterpenoid, Asiatic acid is reported to restore the levels of innate antioxidants in STZ- diabetes rats through modulation of GST, SOD, and glutathione peroxidase (GPx) and thereby inhibiting the lipid peroxidation [144]. Similarly, derivatives of glycyrrhetic acid exert hepatoprotection [85], corosolic acid revert oxidative stress [145], arjunolic acid inhibits arsenic induced organ damage [20], CCl_4-induced hepatotoxicity and STZ-induced diabetes in preclinical evaluations through various animal models. These protective effects are mediated either through free radical scavenging effects of these drugs or through restoration of the innate antioxidants [74, 146].

Cancer chemotherapy induced oxidative stress is the primary reason for organ damage. Concurrent administration of potent antioxidants like pentacyclic triterpenoids can minimize the chemotherapy-induced oxidative stress. Pentacyclic triterpenoids and their derivatives possess antioxidant potential [60, 74, 103, 121-123, 125, 147-149]. In addition to such potent antioxidant effects, pentacyclic triterpenoids also possess cytoprotective effect and can sensitize the cancer cells to cytotoxic actions of chemotherapy. This dual effect through interaction with multiple biomolecules provides unique advantage in using pentacyclic triterpenoids as adjuvants to cancer chemotherapy [37, 150-154].

3.1.4 Protein kinase C pathway inhibition for cytoprotection

Protein kinase C (PKC) including of serine/threonine kinases that manipulate a wide range of cellular processes and are involved in VCAM-1 induction [155]. Based on the structure and cofactor regulations PKC is classified in three different groups: first is diacylglycerol and Ca^{2+} dependent conventional isoforms like α, βI, βII

and γ, second is diacylglycerol dependant but Ca^{2+} independent novel PKC isoform like δ, ε, η, θ, and μ, third is diacylglycerol and Ca^{2+} independent atypical isoforms like ι, λ and ζ [156]. In addition to all isoform of PKC family, PKC δ is a component which is activated in a calcium independent manner [157-158] and extensively articulated in diverse tissues and has been implicated in a overabundance of cellular processes together with proliferation and apoptosis [159-160]. PKC δ is required for the survival and proliferation of cancer cells and not for the normal cell with this hypothesis suppression of PKC δ leads to cell injury and death in tumors. PKC δ suppressing agents will lead to normal tissue specific protective agents in chemotherapy [161]. Moreover, silencing to the PKC family sub members may also sensitize the chemotherapy resistant cancer cells through phosphorylation to p-gp receptor [162].

Pentacyclic triterpenoids like betulinic acid, plantanic acid, oleanolic acid, asiatic acid, glycyrrhetic acid, ursolic acid, uvaol, asiaticoside and their derivatives possess PKC modulatory activity which is supposed to contribute to their anticancer activity [163-165]. Maslinic acid was exerts anticancer potential in the Epstein-Barr virus-induced cancer in Raji cells by inhibiting the PKC pathway [166]. A recent study proves that maslinic acid, oleanolic acid and ursolic acid directly inhibit the βI, ζ, and δ isoforms of PKC in phorbol 12-myristate 13-acetate-induced Raji cells in dose dependant manner [167]. Similar inhibitory activity is reported for lupeol, alpha amyrin and their derivatives against cyclic AMP dependant and Ca^{2+} dependant PKC in the rat liver and brain cells where they produce anti-inflammatory activity [168]. Arjunolic acid revert oxidative stress and hyperglycaemia exert by PKC activation in diabetic and its related complications [169].

In addition to its role in cancer cell growth, PKC δ is associated with the process of inflammation. The PKC inhibiting ability of pentacyclic triterpenoids thus can offer an added advantage if used as adjuvant to chemotherapy. PKC inhibition may sensitize the cancer cells to cytotoxic agents and thereby minimize the dose of chemotherapeutic agent.

3.1.5 Longevity cytoprotective pathways

The turnover of oxidative radicals is tightly controlled by different molecular pathways. Such fine control of oxidative stress determines the process of aging, detoxification and cell death [170]. The molecular pathways controlling oxidative stress contribute to longevity of the organisms. Certain components of these pathways determine responses of normal cells to the drugs, oxidative stress, chemicals and pathogens [171]. Cancer itself minimizes the survival time [172], moreover the chemotherapeutic agents treat the cancer but simultaneously they also responsible to the aberrant toxic effects on the vital organ as well as the immunity [1, 92, 94, 100, 173].

Oxidative stress, disease condition as well as impaired functionality of vital organs ultimately results in the shorting of life [174]. The cytoprotective mechanisms of pentacyclic triterpenoids include their interactions with components of longevity pathways like mitochondrial and endoplasmic reticulum protein response like heat shock proteins (HSP), ROS responses like SOD, xenobiotic detoxification response like GST, insulin/IGF-1 signaling, autophagy and transcriptional factor like NrF2 [175-178]. The reports on betulinic acid induced inhibition DMBA-induced carcinogesis [142], oleanolic acid related restoration of GST activity [123], and other pentacyclic triterpenoids associated cell signal transduction through SOD [95, 179] etc. show their ability to affect longevity pathways. Similarly, cytoprotection exerted by celastrol through heat shock proteins [24, 180], avicin induced selective apoptosis and autophagy in tumor cells and reversal of the resistance of the cancer cell to cytotoxic drugs [181] indicate modulation of longevity pathways by pentacyclic triterpenoids.

Though the cell longevity is driven by diverse signaling cascades like HSP, SOD, GST, IGF-1, JNK and Nrf2, the pentacyclic triterpenoids possess ability to modulate majority of these signaling pathway. In addition to these, they also modulate JNK [72, 182]. Such multi functionality of pentacyclic triterpenoids may add to longevity in the cancer patients. Certain studies in this regard have concluded in agreement with the claims on longevity induced by pentacyclic triterpenoids [178, 183].

Conclusion:

The naturally occurring pentacyclic triterpenoids and their derivatives may prove to be safe, economic and easily available agents which exert selective toxicities towards cancer cells while protecting the normal ones. The biomolecules involved in the survival, growth and resistance to chemotherapy appear to be accessible to the actions of these multifunctional agents. The molecular pathway related to NFκ-B, NrF2, innate antioxidants, protein kinases and longevity pathways are targetable by the pentacyclic triterpenoids. This unique globularity in the actions of pentacyclic triterpenoids along with their selective cytotoxicity towards cancer cells point towards their substantial role as adjuvants to cancer chemotherapy [67,105-106, 184-187]. Systematic investigations on adjuvant like role of pentacyclic triterpenoids in cancer chemotherapy could deliver agents that can be used as routine additives to cancer therapy. In addition to monotargeted novel treatment approaches, the use of validated adjuvants like pentacyclic triterpenoids can provide sustainable approach in minimizing the doses of chemotherapeutic agents without affecting

their cytotoxicity against the cancer cells. Pentacyclic triterpenoids and their derivatives hold a great promise as adjuvants in cancer chemotherapy.

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Conflict of interest:

Authors are disclosing that there are no conflicts of interest.

Figure legend:

The molecular targets on which pentacyclic triterpenoids like BET, Betulinic acid; BOS, Boswellic acid; ARJ, Arjunolic acid; MAS, Maslinic acid; MAD. Madecassic acid; CEL, Celastrol; PRI, Pristimerin; OLE, Oleanolic acid; TAR, Tarexerol acetate; ASI, Asiatic acid; MAN, Maniladione; BAR, Bartogenic acid; TOR, Tormentic acid; GLY, Glycyrrhetic acid; COR, Corosolic acid; HBA, 23-Hydroxy betulinic acid; EUS, Escaphic acid; URS, Ursolic acid; CEN, Cenothic acid; LUP, Lupeol are acting with which they will exert cytoprotective adjuvants effect to cancer chemotherapy.

List of abbreviations:

Nuclear factor erythroid-derived like 2 (NrF2), Nuclear factor kappa B (NFκ-B), Protein kinase C (PKC), Kelch-like ECH-associated binding protein (Keap-1) Glutathion S transferase (GST), Superoxide dismutase (SOD), Catalase (CAT), NAD(P)H dehydrogenase (quinone 1) (NQO1), Heme oxygenase 1(HO-1), Tumour necrosis factor-α (TNF-α), Intercellular Adhesion Molecule 1(ICAM), 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridin (MPTP), Antioxidant response element (ARE), Vascular cell adhesion protein 1 (VCAM-1), streptozotocin (STZ), Mitogen-activated protein kinases (MAPK), Cyclooxygenase-2 (COX-2), Inducible nitric oxide synthase (iNOS), Lipopolysccharide (LPS), Interleukin (IL), Matrix metallopeptidase 9 (MMP-9), Glutathione (GSH), Glutathione peroxidase (GPx), Heat shock proteins (HSP), Reactive oxygen species (ROS), Insulin growth factor-1 (IGF-1), c-Jun N-terminal kinase (JNK).

References:

[1] M. Mohan, S. Kamble, P. Ghadi, S. Kasture, *Food. Chem. Toxicol.*, 2010, **48**, 436-440.

[2] X. Zhang, M. Su, Y. Chen, J. Li, W. Lu, *Molecules*, 2013**, 18**, 6491-6503.

[3] M. Singh, P. Chaudhry, F. Fabi, E. Asselin, *BMC Cancer*, 2013, **13**, 1-9.

[4] D. M. K. Keefe, E. H. Bateman, *Nat. Rev. Clin. Oncol.,* 2012, **9**, 98-109.

[5] R. Sarin, *J Cancer Res. Ther.*, 2008, **4**, 1-3.

[6] C. Pisano, S. C. Cecere, M. D. Napoli, C. Cavaliere, R. Tambaro, G. Facchini, C. Scaffa, S. Losito, A. Pizzolorusso, S. Pignata, *J. Drug Delivery*, 2013, **2013**, 1-12.

[7] C. R. Culy, C.M. Spencer, *Drugs*, 2001, **61**, 641-684.

[8] N. Tas, B. Bakar, M. O. Kasimcan, S. Gazyagci, S. Ayva, K. Kılınc, C. Evliyaoglu, *Int. J. Care Injured*, 2010, **41**, 1068-1074.

[9] W. Caceres, L. Baez, I Aponte, N. Rodriguez, A. Maldonado, *Bol. Asoc. Med. P. R.*, 1997, 89, 184-188.

[10] J. Auta, E. Costa, J. Davis, A. Guidotti, *Neuropharmacology*, 2004, **46**, 397-403.

[11] Y. S. Shin, S. J. Song, Kang, H. S. Hwang, Y. S. Jung, C. H. Kim, *J Appl Toxicol.*, 2013, http://dx.doi: 10.1002/jat.2852.

[12] K. El-Bayoumy, *Mutation Research*, 2001, **475**, 123-139.

[13] I. Cordero-Herrera, S. Cuello, L. Goya, Y. Madrid, L. Bravo, C. Camara, S. Ramos, *Food Chem. Toxicol.*, 2013, **59**, 554-563.

[14] Das, Bornita, Chaudhuri, Keya, *RSC Adv.,* 2014, DOI: 10.1039/C4RA00338A.

[15] P. Paul, M. K. Unnikrishnan, A.N. Nagappa, *Indian Journal of Natural Products and Resources*, 2011, **2**, 137-150.

[16] T. K. Yim, W. K. Wu, W.F. Pak, K.M. Ko, *Phytother. Res.*, 2001, **15**, 589-592.

[17] E. Eksioglu-Demiralp, E. R. Kardas, S. Ozgul, T. Yagc, H. Bilgin, O. Sehirli, F. Ercan, G. Sener, *Phytother. Res.*, 2010, **24**, 325-332.

[18] L. M. Schuchter, *Oncology*, 1997, **11**, 505-512.

[19] C. Chandramu, R. D. Manohar, D. G. L. Krupadanam, R. V. Dashavantha, *Phytother. Res.*, 2003, **17**, 129-134.

[20] B. Mahajan, S. C. Taneja, V.K. Sethi, K. L. Dhar, *Phytochemistry*, 1995, **39**, 453-455.

[21] P. Manna, M. Sinha, P. Pal, P. C. Sil, *Chemico-Biological Interactions*, 2007, **170**, 187-200.

[22] A. R. Marti´n, R. D. Va´zquez, A. Ferna´ndez-arche, V. Ruiz-gutie´rrez, *Free Radical Research*, 2006; **40**, 295-302.

[23] O. A. Oyedeji, A.J. Afolayan, *Pharmaceutical Biol.*, 2005, **43**, 249-252.

[24] J. Lee, T. H. Koo, H. Yoon, H. S. Jung, H. Z. Jin, K. Lee, X. Y. Hong, J.J. Lee, *Biochemical Pharmacology*, 2006, **72**, 1311-1321.

[25] A. Salminen, M. Lehtonen, T. Paimela, K.; Kaarniranta, *Biochemical and Biophysical Research Communications*, 2010, **394**, 439-442.

[26] D.Q. Luo, *et al.*, *Pest Manag. Sci.*, 2005, **61**, 85.

[27] R. Rodrıguez-Rodrıguez,M. D. Herrera, J. S. Perona, V. RuizGutierrez, *British Journal of Nutrition*, 2004, **92**, 635-642.

[28] S. Chauhan, A. Singh, *Rev. Inst. Med. Trop. Sao Paulo*, 2011, **53**, 265-270.

[29] M. Bonfill, S. Mangas, R. M. Cusido, L. Osuna, M.T. Pinol, J. Palazon, *Biomed. Chromatogr.*, 2005, **20**, 151-153.

[30] M. Ukiya, T. Akihisa, H. Tokuda, H. Suzuki, T. Mukainaka, E. Ichiishi, Y. Kasahara, H. Nishino, *Cancer Letters*, 2002, **177**, 7-12.

[31] K. R. Patil, C. R. Patil, R. B. Jadhav, V. K. Mahajan, P. R. Patil, P.S. Gaikwad, *E CAM*, 2011, **2011**, 1-7.

[32] J. H. Chen, Z. H. Xia, R. X. Tan, *J. Pharmaceutical and Biomed. Anal,* 2003, **32**, 1175-79.

[33] C. Sabbioni, R. Mandrioli, A. Ferranti, F. Bugamelli, M. A. Saracino, G.C. Forti, S. Fanali, M. A. Raggi, *J. Chromatography A*, 2005, **1081**, 65-71.

[34] N. Bai, K. He, M. Roller, B. Zheng, Z. Chen, Z. Hao, T. Peng, A. Zheng, *J. Agric. Food Chem*, 2008, **56**, 11668-11674.

[35] W. Ye, N. Ji, S. Zhao, J. Lio, T. Ye, *Phytochemistry*, 1996, **42**, 799-802.

[36] H. Xu, F. Zeng, M. Wan, K. Sim, *J. Natural Products*, 1996, **59**, 7643-7645.

[37] A. Shukla, K. Kaur, P. Ahuja, *Online International Interdisciplinary Research Journal*, 2013, **3**, 9-14.

[38] S. Lee, B. Tin, K. C. Liu, *Phytochemistry*, 1996, **43**, 847-851.

[39] E. Melliou, P. Magiatis, L. Skaltsounis, *J. Agric. Food Chem.*, 2003, **51**, 1289-1292.

[40] B. B. Aggarwal, S. Shishodia, *Biochemical Pharmacology*, 2006, **71**, 1397-1421.

[41] I. M. Copple,C. E. Goldring, N. R. Kitteringham, B. K. Park, *Toxicology*, 2008, **246**, 24-33.

[42] Y. Li, S. W. A. Himaya, S. Kim, *Molecules*, 2013, **18**, 7886-7909.

[43] S. Jager, H. Trojan, T. Kopp, M. N. Laszczyk, A. Scheffler, *Molecules*, 2009, **14**, 2016-2031.

[44] P. K. Chaturvedi, K. Bhui, Y. Shukla, *Cancer Letters*, 2008, **263**, 1-13.

[45] Y. Takada, B. B. Aggarwal, *J. Immunol.*, 2003, **171**, 3278-3286.

[46] H. Kasperczyk, K. L. Ferla-Bruhl, M. A. Westhoff, L. Behrend, R. Zwacka, K. Debatin, S. Fulda, *Oncogene*, 2005, **24**, 6945-6956.

[47] F. B. Mullauer, J. H. Kessler, J. P. Medema, *Apoptosis*, 2009, **14**, 191-202.

[48] J. J. Yoon, Y.J. Lee, J. S. Kim, D. G. Kang, H. S. Lee, *Biochemical and Biophysical Research Communications*, 2010, **391**, 96-101.

[49] Q. Lu, N. Xia, H. Xu, L. Guo, P. Wenzel, A. Daiber, T. Munzel, U. Forstermann, H. Li, *Nitric Oxide*, 2011, **24**, 132-138.

[50] T. Akihisa, K. Tabata, N. Banno, H. Tokuda, R. Nishihara, Y. Nakamura, Y. K. Imura, K. Y. Asukawa, T. Suzuki, *Biol. Pharm. Bull.*, 2006, **29**, 1976-1979.

[51] S. Roy, S. Khanna, A. V. Krishnaraju, G.V. Subbaraju, T. Yasmin, D. Bagchi, C. K. Sen, *Antioxidants and Redox Signaling*, 2006, **8**, 653-660.

[52] Y. Takada, H. Ichikawa, V. Badmaev, B. B. Aggarwal, *J. Immunol*, 2006, **176**, 3127-3140.

[53] P. Manna, M. Sinha, P. C. Sil, *Arch Toxicol*, 2008, **82**, 137-149.

[54] J. Ghosh, J. Das, P. Manna, P. C. Sil, *Toxicology in Vitro*, 2008, **22**, 1918-1926.

[55] J. Ghosh, J. Das, P. Manna, P. C. Sil, *Toxicol.*, 2010, **268**, 8-18.

[56] P. Manna, J. Das, J. Ghosh, P. C. Sil, *Free Radical Biology & Medicine*, 2010, **48**, 1465-1484.

[57] X. Wen, P. Zhang, J. Liu, L. Zhang, X. Wu, P. Ni, H. Sun, *Bioorg. & Med.Chem. Letters*, 2006, **16**, 722-726.

[58] Y. W. Hsum, W. T. Yew, P. L. V. Hong, K. Soo, L. S. Hoon, Y. C. Chieng, L. Y. Mooi, *Planta Med.*, 2011, **77**, 152-157.

[59] A. H. Shaikh, S. N. Rasool, M. A. Kareem, G. S. Krushna, P. M. Akhtar, K. L. Devi, *J. Med. Food*, 2012, **15**, 741-746.

[60] W. H. Yap, S. K. Khoo, H. S. K. Ho, Y. M. Lim, *Biomedicine & Preventive Nutrition*, 2012, **2**, 51-58.

[61] M. J. Yin, Y. Yamamoto, R. B. Gaynor, *Nature*, 1998, **396**, 77-80.

[62] M. K. Shanmugam, A. H. Nguyen, A.P. Kumar, B. H. K. Tan, G. Sethi, *Cancer Letters*, 2012, **320**, 158-170.

[63] W. Cao, X. Li, X. Zhang, Y. Hou, A. Zeng, Y. Xie, S. Wang, *Int. Immunopharmacol,*. 2010, **10**, 723-729.

[64] K. Vohra, G. Pal, S. Gupta, S. Singh, Y. Bansal, *Pharmacologyonline*, 2011, **2**, 440-462.

[65] J. Won, J. Shin, H. Park, H. Jung, D. Koh, B. Jo, J. Lee, K. Yun, K. Lee, *Planta Med*, 2010, **76**, 251-257.

[66] S. P. Preetha, M. Kanniappan, E. Selvakumar, M. Nagaraj, P. Varalakshmi, *Comp. Biochem. & Physiol. Part C*, 2006, **143**, 333-339.

[67] D. He, Q. Xu, M. Yan, P. Zhang, X. Zhou, Z. Zhang, W. Duan, L. Zhong, D. Ye, W. Chen, *BMC Cancer*, 2009, **9**, 1-9.

[68] S. Y. Jang, S. Jang, J. Ko, *Cancer Letters*, 2011, **300**, 57-65.

[69] M. S. Willis, C. Patterson, *Circulation*, 2010, **122**, 1740-1751.

[70] W. Y. Seo, A. R. Goh, S. Ju, H. Y. Song, D. Kwon, J. Jun, B. C. Kim, S. Y. Choi, J. Park, *Biochem. and Biophys. Research Commun*, 2011, **407**, 535-540.

[71] C. Wu, M. Chan, W. Chen, *Mol. Cancer Ther.*, 2005, **4**, 1277-1285.

[72] J. Byun, M. Kim, D. Eum, C. Yoon, W. Seo, K. H. Park, W. Hyun, Y. Lee, J. Lee, M. Yoon, S. Lee, *Mol Pharmacol*, 2009, **76**, 734-744.

[73] J. C. R. Vellosa, N. M. Khalil, V. O. Gutierres, V. Santos, M. Furlan, I. L. Brunetti, O. M. Oliveira, *Brazilian J. Pharmaceutical Sciences*, 2009, **45**, 99-107.

[74] H. Sassa, K. Kogure, Y. Takaishi, H. Terada, *Free Radical Biol. & Med.*, 1994, **17**, 201-207.

[75] R. D. Couch, R. G. Browning, T. Honda, W. G. Gribble, D. L. Wright, M. B. Sporn, A. C. Anderson, *Bioorg & Med. Chem. Letters*, 2005, **15**, 2215-2219.

[76] N. B. Janakiram, C. Indranie, S. V. Malisetty, P. Jagan, V. E. Steele, C. V. Rao, *Pharmaceutical Research*, 2008, **25**, 2151-57.

[77] D. Deeb, X. Gao, H. Jiang, S. A. Dulchavsky, S. C. Gautam, *The Prostate*, 2009, **69**, 851-860.

[77] S. A. Reisman, L. M. Aleksunes, C. D. Klaassen, *Biochemical pharmacology*, 2009, **77**, 1273-1282.

[78] C. R. Patil, R. B. Jadhav, P. K. Singh, S. Mundada, P. R. Patil, *Phytother. Res.*, 2010, **24**, 33-37.

[79] M. Shyu, T. Kao, G. Yen, *J. Agric. Food Chem.*, 2010, **58**, 6110-6118.

[80] A. Jutiviboonsuk, H. Zhang, T.P. Kondratyuk, A. Herunsalee, W. Chaukul, J. M. Pezzuto, H. S. Fong, N. Bunyapraphatsara, *Pharmaceutical Biology*, 2007, **45**, 185-194.

[81] A. Kamboj, A. K. Saluja, *Phcog Rev.*, 2009, **3,** 364-374.

[82] X. Yao, G. Li, Q. Bai, H. Xu, C. Lu, *Int Immunopharmacol.*, 2013, **15**, 316-24.

[83] A. Gnanapragasam, K. K. Ebenezar, V. Sathish, P. Govindaraju, T. Devaki, *Life Sciences*, 2004, **76**, 585-597.

[84] Y. Hsu, P. Kuo, L. Lin, C. Lin, *JPET*, 2005, **313**, 333-344.

[85] H. G. Jeong, H. J. You, S. J. Park, A. Moon, Y. C. Chung, S. K. Kang, H. Chun, *Pharmacological Research*, 2002, **46**, 221-227.

[86] L. Zhang, J. Chen, Y. Gong, J. Liu, L. Zhang, W. Hu, H. Sun, *Chemistry & Biodiversity*, 2009, **6**, 864-874.

[87] K. Y. Lee, O. Bae, S. Serfozo, S. Hejabian, A. Moussa, M. Reeves, W. Rumbeiha, S. D. Fitzgerald, G. Stein, S. Baek, J. Goudreau, M. Kassab, A. Majid, *Stroke*, 2012, **43**, 1632-1638.

[88] K. Yun, J. Kim, K. Lee, S. Jeong, H. Park, H. Jung, Y. Cho, K. Yun, K. Lee, *Int. Immunopharmacol.*, 2008, **8**, 431-441.

[89] E. Y. Vouffo, F. M. Donfack, R. J. Temdie, F. T. Ngueguim, J. H. Donfack, D. D. Dzeufiet, A. B. Dongmo, T. Dimo, *J. Expt. and Integrative Med.*, 2012, **2**, 337-344.

[90] T. J. Thomas, B. Panikkar, A. Subramoniam, M. K. Nair, K. R. Panikkar, *J. Ethnopharmacology*, 2002, **82**, 223-227.

[91] C. Murakami, K. Ishijima, M. Hirota, K. Sakaguchi, H. Yoshida, Y. Mizushina, *Biochimica and Biophysica Acta*, 2002, **1596**, 193-200.

[92] Y. Kim, J. Choi, H. Rim, H. Kang, S. Chang, J. Park, H. Park, J. W. Choi, S. Kim, K. Lee, *Biol. Pharm. Bull.*, 2011, **34**, 906-911.

[93] H. Sheng, H. Sun, *Nat. Prod. Rep.*, 2011, **28**, 543-593.

[94] S. Sohn, H. Rim, Y. Kim, J. Choi, J. Park, H. Park, J.; Choi, S. K. Kim, S. Jeong, K. Lee, *Biol. Pharm. Bull.*, 2011, **34**, 1508-1513.

[95] C. Chang, S. Huang, S. Lin, S. Amagaya, H. Ho, W. Hou, P. Shie, J. Wu, G. Huang, *Food Chemistry*, 2011, **127**, 1131-37.

[96] H. Nishino, K. Kitagawa, A. Iwashima, *Cardnogenesis*, 1984, **5**, 1529- 1530.

[97] S. Saito, S. Nagase, M. Kawase, Y. Nagamura, *Eur. J. Med. Chem.*, 1996, **31**, 557-574.

[98] E. Sohn, D. Kang, H. Lee, *Pharmacol. And Toxicol.*, 2003, **93**, 116-122.

[99] Y. Satomi, H. Nishino, S. Shibata, *Anticancer Research*, 2005, **25**, 4043-4048.

[100] C. S. Lee, Y. J. Kim, M. S. Lee, E. S. Han, S. J. Lee, *Life sciences*, 2008, **83**, 481-489.

[101] N. Banno, T. Akihisha, H. Tokuda, K. Yasukawa, K. Higashihara, M. Ukiya, K. Wantanabe, Y. Kimura, J. Hasegawa, H. Nishino, *Biosci. Biotechnol. Biochem.*, 2004, **68**, 85-90.

[102] K. S. Shim, S. Lee, S. Y. Ryu, Y. K. Min, S. H. Kim, *Phytother. Res.*, 2009, **23**, 1754-1758.

[103] M. Yin, M. Lin, M. Mong, C. Lin, *J. Agric. Food Chem.*, 2012, **60**, 7697-7701.

[104] Y. Xu, R. Ge, J. Du, H. Xin, T. Yi, J. Sheng, Y. Wang, C. Ling, *Cancer Letters*, 2009, **284**, 229-237.

[105] Y. Zheng, F. Zhou, X. Wu, X. Wen, Y. Li, B. Yan, J. Zhang, G. Hao, W. Ye, G. Wang, *Journal of Ethnopharmacology*, 2010, **128**, 615-622.

[106] D. Zhang, C. Shu, J. Chen, K. Sodani, J. Wang, J. Bhatnagar, P. Lan, Z. Ruan, Z. Xiao, *Mol. Pharmaceutics*, 2012**, 9**, 3147-3154.

[107] C. H. George, S. R. Barberini-Jammaers, C. T. Muller, *Expt. Opin. Ther. Patents*, **2008**, **18**, 1-19.

[108] S. Shishodia, S. Majumdar, S. Banerjee, B. B. Aggarwal, *Cancer Research*, 2003, **63**, 4375-4383.

[109] Y. Hsu, P. Kuo, C. Lin, *Life Sciences*, 2004, **75**, 2303-2316.

[110] S. Senthil, G. Chandramohan, K. V. Pugalendi, *Int. J.Cardiol.*, 2007, **119**, 131-133.

[111] K. Takada, T. Nakane, K. Masuda, H. Ishii, *Phytomedicine*, 2011, **17**, 1114-1119.

[112] L. Vidya, P. Varalakshmi, *Fitoterapia*, 2000, **71**, 535-543.

[113] R. Saleem, S. I. Ahmad, M. Ahmed, Z. Faizi, S. Zikr-ur-rehman, M. Ali, S. F. Aizi, *Biol. Pharm. Bull.*, 2003, **26**, 41-46.

[114] N. Nigam, S. Prasad, J. George, Y. Shukla, *Biochemical and Biophysical Research Communications*, 2009, **381**, 253-258.

[115] K. T. Liby, M. M. Yore, M. B. Sporn *Nature Reviews*, 2007, **7**, 357-369.

[116] H. Merikallio, P. Paakko, V. L. Kinnula, T. Harju, Y. Soini, *Human Pathology*, 2012, **43**, 577-584.

[117] V. O. Tkachev, E. B. Menshchikova, N. K. Zenkov, *Biochemistry (Moscow)*, 2011, **76**, 407-422.

[118] T. W. Kensler, N. Wakabayashi, *Carcinogenesis*, 2010, **31**, 90-99.

[119] J. D. Hayes, M. McMahon, S. Chowdhry, A. T. Dinkova-Kostova, *Antioxidants and Redox Signaling*, 2010, **13**, 1714-1748.

[120] K. Jung, M. Kwak, *Molecules*, 2010, **15**, 7266-7291.

[121] K. Liby, T. Hock, M. M. Yore, N. Suh, A. E. Place, R. Risingsong, C. R. Williams, D. B. Royc, T. Honda, Y. Honda, G. W. Gribble, N. Hill-Kapturczak, A. Agarwal, M. B. Sporn, *Cancer Rec*, 2005, **65**, 4789-4798.

[122] L. Yang, N. Y. Calingasan, B. Thomas, R. K. Chaturvedi, M. Kiaei, *Plos ONE*, 2009, **4**, 1-14.

[123] M. B. Sporn, K. T. Liby, G. W. Gribble T. Honda, R. M. Kral, C. J. Meyer, *US Pat.*, 8129 429 B2, 2012.

[124] J. D. Hayes, M. McMahon, S. Chowdhry, A. T. Dinkova-Kostova, *Antioxidants and Redox Signaling*, 2010, **13**, 1714-1748.

[125] M. B. Sporn, K. T. Liby, M. M. Yore, L. Fu, J. M. Lopchuk, G. W. Gribble, *J. Nat. Prod.*, 2011, **74**, 537-545.

[126] B. Rayet, C. Gelinas, *Oncogene*, 1999, **18**, 6938-6947.

[127] S. Prasad, J. Ravindran, B. B. Aggarwal, *Mol Cell Biochem*, 2010, **336**, 25-37.

[128] A. D. J. Van, S. J. Martin, T. Kafri, D. R. Green, I. M. Verma, *Science*, 1996, **274**, 787-789.

[129] C. Y. Wang, M. W. Mayo, A. S. J. Baldwin, *Science*, 1996, **274**, 784-787.

[130] Y. Yamamoto, M. J. Yin, K. M. Lin, R. B. Gaynor, *J. Biol. Chem*, 1999, **274**, 27307-27314.

[131] Y. Yamamoto, R. B. Gaynor, *The J. Clin. Investig*, 2001, **107**, 135-142.

[132] A. Kumar, B. A. Shah, S. Singh, A. Hamid, S. K. Singh, V. K. Sethi, A. K. Saxena, J. Singh, S. C. Taneja, *Bioorg. & Med. Chem. Letters*, 2012, **22**, 431-435.

[133] S. Prasad, E. Madan, N. Nigam, P. Roy, J. George, J. Shukla, *Cancer Biology & Therapy*, 2009, **8**, 1632-1639.

[134] J. K. Kundu, Y. Surh, *Pharm Res*, 2010, **27**, 999-013.

[135] V. R. Yadav, S. Prasad, B. Sung, R. Kannappan, B. B. Aggarwal, *Toxins*, 2010, **2**, 2428-2466.

[136] S. M. Attia, *Oxidative Medicine and Cellular Longevity*, 2010, **3**, 238-253.

[137] C. Houée-Levin, K. Bobrowski, *Journal of proteomics*, 2013, **92**, 51-62.

[138] O. O. Shevchuk, E. A. Posokhova, L. A. Sakhno, V. G. Nikolaev, *Exp Oncol*, 2012, **34**, 314-322.

[139] L. Bruton, K. Parker, I. Buxton, in *Goodman and Gilman's annual of pharmacology and therapeutics*, 11th ed., The mcGrow-Hill companies: USA, 2008, pp. 867-888.

[140] H. Mohan, in *The textbook of pathophysiology*, 5th ed., Jaypee brother's medical publishers (P) ltd: India, 2005, pp.38-41 .

[141] I. Bouhlel, K. Valenti, S. Kilani, I. Skandrani, M.B. Sghaier, A. Mariotte, M. Dijoux-Franca, K. Ghedira, I. Hininger-Favier, F. Laporte, *Toxicology in Vitro*, 2008, **22**, 1264-1272.

[142] R. Kaur, S. Arora, *Free Radical Biology and Medicine*, 2013, **65**, 131-142.

[143] M. Sánchez, C. Theoduloz, G. Schmeda-Hirschmann, I. Razmilic, T. Yáñez, J. A. Rodríguez,. *Life Sciences*, 2006, **79**, 1349-1356.

[144] V. Ramachandran, R. Saravanan, *Journal of Functional Foods*, 2013, **5**, 1077-1087.

[145] Y. Yamaguchi, K. Yamada, N. Yoshikawa, K. Nakamura, J. Haginaka, M. Kunitomo, *Life Sciences*, 2006, **79**, 2474-2479.

[146] P. Manna, J. Ghosh, J. Das, P. C. Sil, *Toxicology and Applied Pharmacology*, 2010, **244**, 114-129.

[147] L. I. Somova, F. O. Shode, P. Ramnanan, A. Nadar, *J. Ethnopharmacology*, 2003, **84**, 299-305.

[148] H. S. Chung, *J. Food Sci. Nutr.*, 2009, **14**, 49-53.

[149] T. Morita, *Am. J. Hypertension*, 2010, **23**, 821.

[150] P. Bigoniya, A. Shukla, C. S. Singh, *Int. J. Phytomedicine*, 2010, **2**, 240-254.

[151] X. Peng, J. Liu, Z. Han, X. Yuan, H. Luo, M. Qiu, *Food Chemistry*, 2013, **141**, 920-926.

[152] T. B. Nguelefack, H. K. Mbakam, L. K. Tapondjou, P. Watcho, E. P. Nguelefack-Mbuyo, B. K. Ponou, A. Kamanyi, H. A. Park, *Archives of Pharmacal Research*, 2011, **34**, 543-550.

[153] C. Grace-Lynn, I. Darah, Y. Chen, L. Y. Latha, S. L. Jothy, S. Sasidharan, *Molecules*, 2012, **17**, 11185-11198.

[154] A. Manosroi, P. Jantrawut, E. Ogihara, A. Yamamoto, M. Fukatsu, K. Yasukawa, H. Tokuda, N. Suzuki, J. Manosroi, T. Akihisa, *Chemistry and Biodiversity*, 2013, **10**, 1448-1463.

[155] P. J. Parker, J. Murray-Rust, *J Cell Sci*, 2004, **117**, 131-132.

[156] S. Yan, E. Harja, M. Andrassy, T. Fujita, A. M. Schmidt, *Journal of the American College of Cardiology*, 2006, **48**, A47-A55.

[157] W. S. Liu, C. A. Heckman, *Cell Signal*, 1998, **10**, 529-542.

[158] U. Kikkawa, H. Matsuzaki, T. Yamamoto, *J. Biochem*, 2002, **132**, 831-839.

[159] T. A. De Vries-Seimon, A. M. Ohm, M. J. Humphries, M. E. Reyland, *J. Biol. Chem.*, 2007, **282**, 22307-22314.

[160] M. J. Humphries, A. M. Ohm, J. Schaack, T. S. Adwan, M. E. Reyland, *Oncogene*, 2008, **27**, 3045-3053.

[161] N. Pable, Z. Dong, *Oncotarget*, 2012, **3**, 107-111.

[162] L. Zhao, H. Xu, J. Qu, W. Zhao, Y. Zhao, J. Wang, *Asian Pacific Journal of Cancer Prevention*, 2012, **13**, 3631-3636.

[163] T. Fujioka, Y. Kashiwada, R. E. Kilkuskie, L. M. Cosentino, L.M. Ballas, J. B. Jiang, W. P. Janzen, I. S. Chen, K. H. *J. Nat. Prod.*, 1994, **57**, 243-247.

[164] B. H. Wang, G. M. Polya, *Phytochemistry*, 1996, **41**, 55-63.

[165] L. Moon, Y. M. Ha, H. J. Jang, H. S. Kim, M. S. Jun, Y. M. Kim, Y. S. Lee, D. H. Lee, K. H. Son, H. J. Kim, H. G. Seo, J. H. Lee, Y. S. Kim, K. C. Chang, *J.Ethnopharmacology*, 2011, **133**, 336-344.

[166] L. Y. Wahab, N.A. Lajis, A. M. *Chem Biodivers*, 2010, **7**, 1267-1275.

[167] L. Y. Mooi, W. T. Yew, Y. S. Hsum, K. K. Soo, L. S. Hoon, Y. C. Chieng, *Asian Pacific Journal of Cancer Prevention*, 2012, **13**, 1177-1182.

[168] M. Hasmeda, G. Kweifio-Okai, T. Macrides, G. M. Polya, *Planta Med.,* 1999, **65**, 14-18.

[169] P. Manna, P. C. Sil, *Free Radical Research*, 2012, **46**, 815-830.

[170] K. N. Lewis, J. Mele, J.D. Hayes, R. Buffenstein, *Integ. & Comp. Biol.*, 2010, **50** 829-843.

[171] D. E. Shore, G. Ruvkun, *Trends in Cell Biology*, 2013, **13**, 409-420.

[172] F. Fallah-Rostami, M. A. Tabari, B. Esfandiari, H. Aghajanzadeh, M. Y. Behzadi, *N Am J Med Sci.*, 2013, **5**, 207-212.

[173] S. E. Jang, E. H. Joh, Y. T. Ahn, C. S. Huh, M. J. Han, D. H. Kim, *Immunopharmacol Immunotoxicol*, 2013, **35**, 396-402.

[174] M. Maulik, D. Mc Fadden, H. Otani, M. Thirunavukkarasu, N. L. Parinandi, *Oxidative Medicine and Cellular Longevity*, 2013, **2013**, 1-3.

[175] D. E. Shore, C. E. Carr, G. Ruvkun, *PLoS Genet*, 2012, **8**, 1-15.

[176] M. T. Crow, *Circ. Res.*, 2004, **95**, 953-95.

[177] F. Madeo, N. Tavernarakis, G. Kroemer, *Nature Cell Biology*, 2010, **12**, 842-846.

[178] G. P. Sykiotis, J. G. Habeos, A. V. Samuelson, D. Bohmann, *Curr. Opin. Clin. Nutr. Metab. Care.*, 2011, **14**, 41-48.

[179] Y. Huang, J. Li, Q. Cao, S. Yu, L. Xiong-Wen, Y. Jin, L. Zhang, Y. Zou, J. Ge, *Life Sciences*, 2006, **78**, 2749-2757.

[180] S. D. Westerheide, J. D. Bosman, B. N. A. Mbadugha, T. L. A. Kawahara, G. Matsumoto, S. Kim, W. Gu, J. P. Devlin, R. B. Silverman, R. I. Morimoto, *The Journal of Biological Chemistry*, 2004, **279**, 56053-56060.

[181] H. Wang, V. Haridas, J. U. Gutterman, Z. Xu, *Communicative & Integrative Biology*, 2010, **3**, 205-208.

[182] T. Rabi, . Banerjee, *Molecular Carcinogenesis*, 2008, **47**, 415-423.

[183] C, Stack, D. Ho, E. Wille, N. Y. Calingasan, C. Williams, K. Liby, M. Sporn, M. Dumont, M. F. Beal, *Free Radic Biol Med.*, 2010, **49**, 147-158.

[184] M. L. Hyer, R. Croxton, M. Krajewska, *Cancer Research*, 2005, **65**, 4799-4808.

[185] V. H. Villar, M. Gomez, O. Vogler, J. M. Serra, J. Martin, V. Ruiz-Gutierrez, F. Barcelo, R. Alemany, *Abstract Chemistry and Physics of Lipids*, 2010, **163S**, S57-S59.

[186] K. Liby, T. Honda, C. R. Williams, *Mol Cancer Ther.*, 2007, **6**, 2113-2119.

[187] V. Zuco, R. Supino, S. C. Righetti, L. Cleris, E. Marchesi, C. Gambacorti-Passerini, A. Formelli, *Cancer Letters*, 2002, **175**, 17-25.

Figure 1: Molecular targets with which pentacyclic triterpenoids prove its multifunctional adjuvants effect

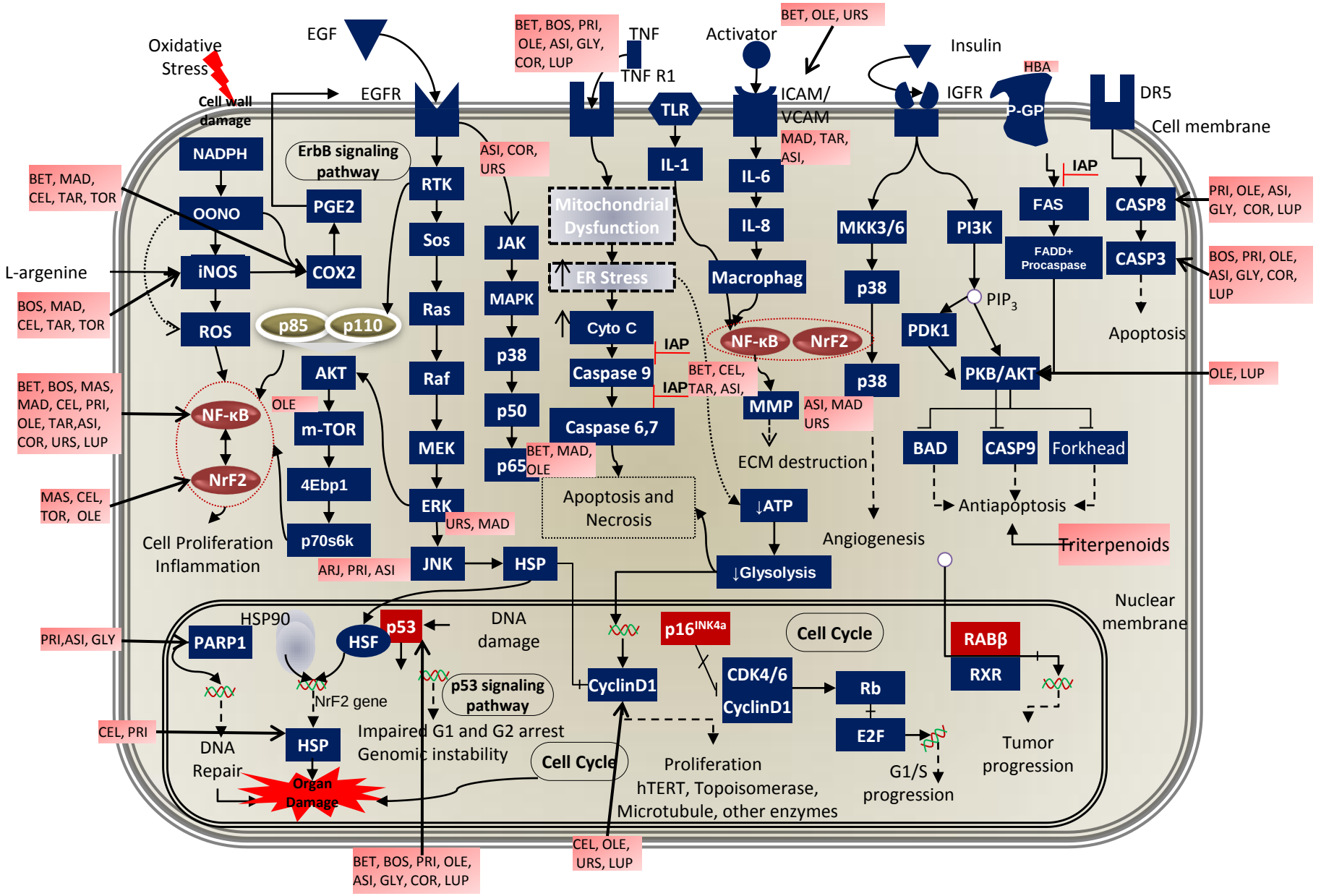
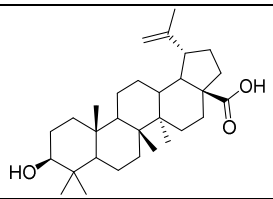
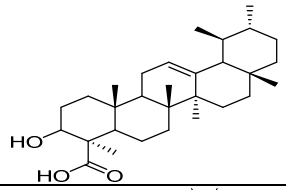
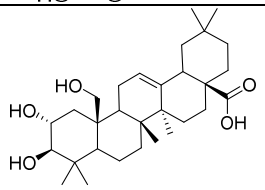
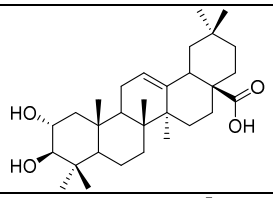
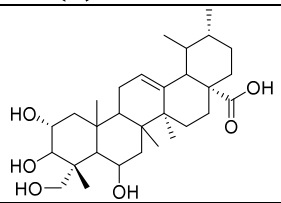
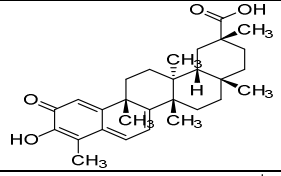
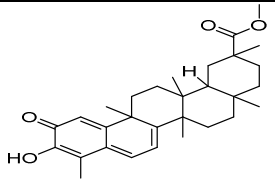
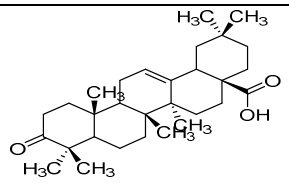
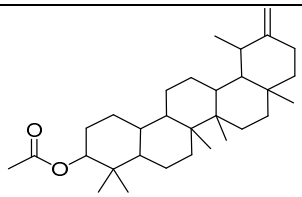
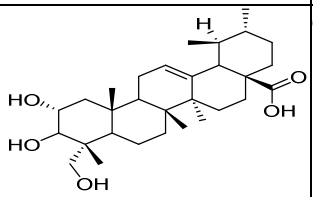
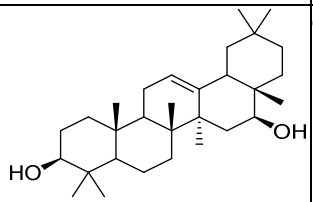
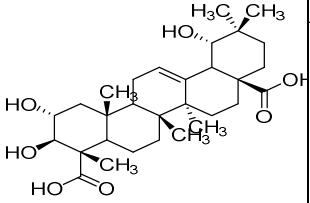
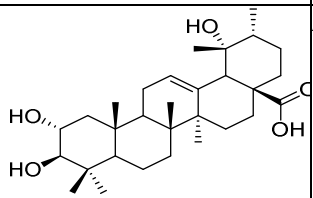
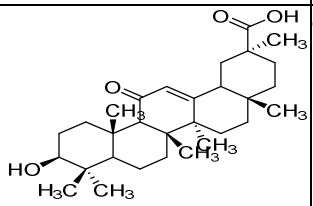
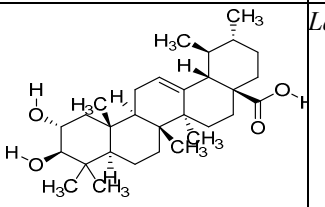


Table 1: Biological sources, chemical structures and parts of plants from which important pentacyclic triterpenoids are extracted

S. no.	Name of tritepenoid	Structure of triterpenoid	Source	Parts used for extraction	Reference
1	Betulinic acid		*Vitex negundo* L.	Leaves of *Vitex negundo* L.	Chandramu *et al*., 2003
2	Boswellic acid		*Boswellia serrata*	Gum resins of *Boswellia serrata*	Mahajan *et al*., 1995
3	Arjunolic acid		*Terminalia arjuna*	Bark	Manna *et al*., 2007
4	Maslinic acid		Orujo olive oil	Oil	Marti´n *et al*., 2006
5	Madecassic acid		*Centella asiatica* (L.)	Essential oil of *Centella asiatica* (L.)	Oyedeji and Afolayan, 2005
6	Celastrol		*Celastrus orbiculatus*	Root of god thunder vine (*Celastrus orbiculatus*)	Lee *et al*., 2006; Salminen *et al*., 2010
7	Pristimerin		*Celastrus hypoleucus*	Roots of *Celastrus hypoleucus*	Lau *et al*., 2005
8	Oleanolic acid		*Orujo olive oil*	Olive oil	Rodriguez-Rodriguez *et al*., 2004

9	Tarexerol acetate		*Codieaum variegatum*	Bark of *Codieaum variegatum*	Chauhan and Singh, 2011
10	Asiatic acid		*Centella asiatica* (L) Urb	Whole plant of *Centella asiatica* (L) Urb	Bonfill *et al*., 2006
11	Maniladiol		*Chrysanthemum morifolium*	Flowers of *Chrysanthemu-m morifolium*	Ukiya *et al*., 2002
12	Bartogenic acid		*Barringtonia racemosa* Roxb	Fruits of *Barringtonia racemosa* Roxb	Patil *et al*., 2011
13	Tormentic acid		*Perilla frutescens* (L.) Britt	Leaves of *Perilla frutescens* (L.) Britt	Chen *et al*., 2003
14	Glycyrrhetic acid		*Glycyrrhiza glabra*	Roots of *Glycyrrhiza glabra*	Sabbioni *et al*., 2005
15	Corosolic acid		*Lagerstroemia speciosa*	Leaves of *Lagerstroemia speciosa*	Bai *et al*., 2008

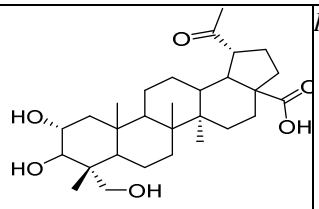
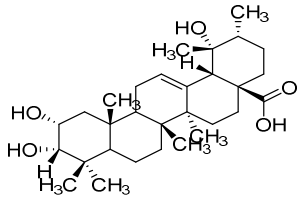
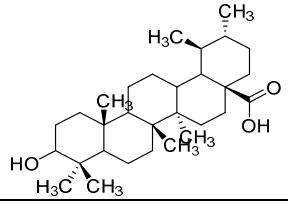
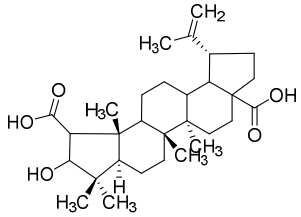
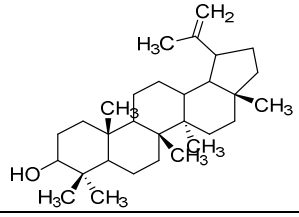
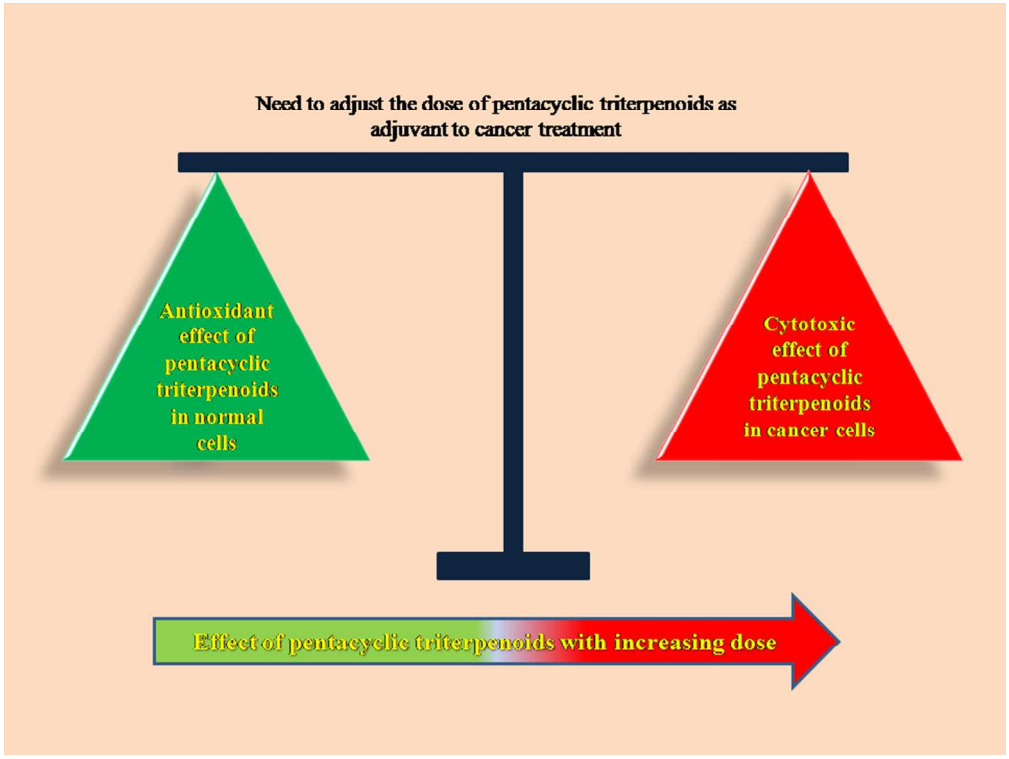
16	23-Hydroxy butulinic acid		*Pulsatilla chinensis*	Roots of *Pulsatilla chinensis*	Ye *et al*., 1996
17	Euscaphic acid		*Geum japonicum* Thunb	Whole plant of *Geum japonicum* Thunb	Xu *et al*., 1996
18	Ursolic acid		*Salvia officinalis and Ocimum sanctum Linn*	Leaves of *Salvia officinalis and* Ocimum sanctum Linn	Shukla *et al.*, 2013
19	Ceanothic acid		*Zizyphus jujuba* Mill. var. *spinosa* (Bunge)	Roots of *Zizyphus jujube*	Lee *et al*., 1996
20	Lupenol		*Cichorium spinosum*	Aerial parts of *Cichorium spinosum*	Melliou *et al*., 2003

Table 2: Pentacyclic triterpenoids acting as organotropic effect on vital organs and its responsible molecular mechanisms

S. no.	Name of compound	Organ protective effect			Molecular mechanisms	References
		Heart	Kidney	Liver		
1	Betulinic acid	✓	✓	✓	NFK-β, p65, p50, Bax, Bcl-2, Bcl-xL, IL-1, COX-2, MMP-9, TNF-α, GSH, MPO, ICAM-1, VCAM-1, and VEGE	Takada and Aggarwal, 2003; Kasperczyk *et al*., 2005; Mullauer and Kessler, 2009; Eksioglu-Demiralp *et al*., 2010; Yoon *et al*., 2010; Lu *et al*., 2011;
2	Boswellic acid	✓	✓	✓	NFK-β, TNF-α, IL-1, Bcl-2, caspase-3, iNOS	Akihisa *et al*., 2006; Roy *et al*., 2006; Takada *et al*., 2006
3	Arjunolic acid	✓	✓	✓	GST, SOD, TNF-α, IL-2, GSH, JNK, Bcl2	Manna *et al*, 2008; Ghosh *et al*., 2008; Ghosh *et al*., 2010; Manna *et al*., 2010
4	Maslinic acid	✓	✓	✓	iGP, NrF2, Cox-2, Ap-1, NFK-β	Wen *et al*., 2006; Hsum *et al*., 2011; Shaikh *et al*., 2012; Yap *et al*., 2012; Yin *et al*., 2012;
5	Madecassic acid	✓	✓	✓	iNOS, COX-2, TNF-α, IL-1, IL-6, NFK-β, p65, ERK, p38	Shanmugam *et al*., 2012; Cao *et al*., 2010; Vohra *et al*., 2011; Won *et al*., 2010
6	Celastrol	✓	✓	✓	NFK-β, AP1, AP2, Bcl-2, Bcl-xL, COX-2, survivin, cyclin D1, MMP9, VEGF, iNOS, Hsp90, VEGFR, NrF2	Lee *et al*., 2006; Preetha *et al*., 2006; He *et al*., 2009; Jang *et al*., 2011; Willis and Patterson, 2010; Seo *et al*., 2011; Brunt *et al*., 2012;
7	Pristimerin	✓	NA	✓	NFK-β, PARP-1, JNK, Bax, p27, Bcl-2, Bcl-xL, caspase-3,-8,-9, HSP-60	Wu *et al*., 2005; Byun *et al*., 2009; Vellosa *et al*., 2009; Sassa *et al*., 1994;
8	Oleanolic acid	✓	✓	✓	NFK-β, m'TOR, caspases-3, -8, and -9, ICAM-1, VEGF, PARP-1, Akt, cyclin-D, p65, NrF2, TNF-α	Yim *et al*., 2001; Couch *et al*., 2005; Janakiram *et al*., 2008; Deeb *et al*., 2009; Reisman *et al*., 2009; Patil *et al*., 2010; Shyu *et al*., 2010
9	Tarexerol acetate	✓	✓	✓	MMP-1, TNF-α, iNOS, COX-2, NFK-β, IL-1, IL-6	Jutiviboonsuk *et al*., 2007; Kamboj and Saluja, 2009; Yao *et al*, 2013
10	Asiatic acid	✓	✓	✓	NFK-β, iNOS, MAPK, caspases-2, -3, -8 and -9, PARP-1, Bcl-2, iGP, JNK, p38, MMP-9, PGE_2, TNF-	Ukiya *et al*, 2002; Gnanapragasam *et al*., 2004; Hsu *et al*., 2005; Jeong *et al*., 2007;

							α, IL-1, IL-6	Zhang *et al*., 2009; Lee *et al*., 2012; Yun *et al*., 2008; Vouffo *et al*., 2012;
11	Maniladiol	NA		NA		NA	-	-
12	Bartogenic acid	NA		NA		NA	PGs and IL-1	Thomas *et al*., 2002; Patil *et al*, 2011;
13	Tormentic acid		✓		✓		✓	α and β DNA polymerase, GSH, NrF2, COX-2, TNF-α, iNOS	Murakami *et al*., 2002; Kim *et al*., 2011; Sheng and Sun, 2011; Sohn *et al*., 2011; Chang *et al*., 2011;
14	Glycyrrhetic acid		✓		✓		✓	cytochrome C, Bcl-2, Bcl-xL, Bak, caspase-3, Caspase-8, PPARγ	Nishino *et al*., 1984; Saito *et al*., 1996; Sohn *et al*., 2003; Satomi *et al*., 2005; Lee *et al*., 2008
15	Corosolic acid		✓		✓		✓	NFK-β, MAPK, IAP-1, caspase-8, -9 and -3, Bcl-2, iEBV-EA	Banno *et al*., 2004; Shim *et al*., 2009; Xu *et al*., 2009; Yin *et al*., 2012;
16	23-Hydroxy butulinic acid	NA		NA		NA		Pgp and MDR	Zheng *et al*., 2010; Zhang *et al*., 2012
17	Euscaphic acid		✓	NA		NA		iα DNA polymerase	Murakami *et al*., 2002; George *et al*., 2008
18	Ursolic acid		✓		✓		✓	NFK-β, p38, MAPK, Bcl-2, Bax, ICAM-1, p53,p21, PKC, Cyclin D1,-D2, EGFR, ERK, TNF-α	Shishodia *et al*., 2003; Hsu *et al*., 2004; Senthil *et al*., 2007; Takada *et al*., 2011
19	Ceanothic acid	NA		NA		NA		-	-
20	Lupenol		✓		✓		✓	NFK-β, survivin, Bax, caspase-3, -8,-9, p53, Cyclin-D, Akt	Vidya and Varalakshmi, 2000; Saleem *et al*., 2003; Nigam *et al*., 2009; Prasad *et al*., 2009.



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