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Insights into anticancerous, antioxidant and anti-inflammatory effects of mangiferin

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Abstract
A naturally occurring C-glucosylxanthone called mangiferin has a wide range of biological activities that make it an excellent candidate for the treatment of many disorders. Due to their special qualities, accessibility, and much lower side effects, natural biologically active molecules have long been the focus of the pharmaceutical industry. Numerous studies have revealed that mangiferin has antioxidant, anti-infection, anti-cancer, anti-diabetic, cardiovascular, neurological, and immunity-boosting activities. Its non-toxicity is particularly crucial. Mangiferin's oral bioavailability and rate of body absorption, however, are both too low for therapeutic application at the moment. Mangiferin integrated polymer systems have been created to increase the solubility, biological action, and bioavailability.

Keywords: Mangiferin, anti-cancer, anti-inflammatory activity

Introduction
Mangiferin, a recently discovered phytochemical with pharmacological activity, is found in a variety of plants, including *Mangifera indica* L. It is a polyphenol (Lv *et al*., 2013) [1] found in many plant species, in particular, those from the Anacardiaceae (Rajendra *et al*., 2013; Hu *et al*., 2013) [2, 3] and Gentianaceae families (Zhang *et al*., 2014) [4]. Since antiquity, Indian Ayurvedic practitioners (Kavitha *et al*., 2013) [5] are found to be using *Salacia chinensis* (saptarangi) (Matkowski *et al*., 2013;Chavan *et al*., 2015; Chellan *et al*., 2014) [6-8] and *Mangifera indica* (mango), which are the two species that harbours significantly high levels of mangiferin. *Salicia chinensis* has been popularly used owing to its hypo-lipidaemic, anti-diabetic, hepatoprotective and antioxidant properties. Now, *Salicia chinensis* can be considered as an over-exploited plant and research is conducted to find out ways to grow the miraculous plant in a more sustainable way to meet the ever increasing demands (Chavan *et al*., 2015) [7]. *Mangifera indica* is used not only in Indian Ayurvedic medicine but has also used in Cuba (Tolosa *et al*., 2013) [9], China (Matkowski *et al*.,2013; Zou *et al*., 2013) [6, 10] and throughout East Asia (Matkowski *et al*.,2013) [6]for its anti-inflammatory, anti-viral, anti-diabetic and anti-cancer properties. Its molecular formula is C19H18O11, and its chemical name is 2-C--D-gluco-pyranosyl-1,3,6,7-tetrahydroxyxanthone. Molecular weight: 422.35, anhydrous melting point: 271 °C (Guha *et al*., 1996) [11].
Mangiferin, also referred to as alpizarin or quinomine, is a member of the organic class of xanthones. Its structure was recognised in 1960s (Nott *et al*., 1967; Bhatia *et al*., 1967) [12, 13]. Mangiferin has just lately been the subject of an X-ray diffraction investigation. It is a polyphenol attached to the glucose residues by an erroneous C-C bond (Faizi *et al*., 2006; da Cruz *et al*., 2008) [14, 15]. A pigment called mangiferin was first discovered in mangoes (*Mangifera indica* L., Anacardisaceae) in 1908 (Nott *et al*., 1967; Wiechowsk *et al*., 1908) [12, 16].
Mangiferin is insoluble in some non-polar solvents, such as n-hexane or diethyl ether(Acosta J *et al*., 2016) [17], but only slightly soluble in ethanol and water. Mangiferin solubility in water is just 0.111 mg/mL (da Rocha Ferreira F *et al*., 2013) [18].
Mangiferin's antiviral (Zheng and Lu, 1990; Zbu *et al*., 1993; Guha *et al*., 1996; Yoosook *et al*., 2000) [19, 20, 11, 21]and anticancer (Guha *et al*., 1996) [11] properties have been reported to have major pharmacological effects. In the last few years, mangiferin's pharmacological effects on the oxidative processes have drawn a lot of interest (Sanchez *et al*., 2000) [22]. Numerous investigations have shown that mangaferin has a wide range of biological functions owing to multiple mechanisms.

A few examples include anti-cancer, antioxidant, anti-inflammatory, anti-diabetic, cardiovascular protection, neuroprotective, antiviral, enhanced immunity, gastroprotective effect, analgesic activity and radioprotection, as demonstrated in mouse experiments. Additionally, anti-allergic capabilities, hepatoprotective action and the neuroprotective impact have also been described (Morozkina*et al*., 2021) [23].

Mangiferin has not shown any genotoxic, clastogen, acute, or embryotoxic effects in studies conducted *in vitro* and *in vivo*. Mangiferin can also withstand the genetic harm brought on by known mutagenic substances (Zhang *et al*., 2014) [4].

Structure

Chemically Mangiferin is C2-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone. C-glucosyl xanthone in its structure contains aromatic ring attached to the C-C bond of the glucose moiety are responsible for its high polarity and water solubility. The catechol ring, free hydroxyl groups, and redoxactive aromatic system due to xanthine moiety contribute towards the anti-oxidant activity of mangiferin. Its prompt iron-chelating property prevents hydroxyl radicals to get involved in Fenton-type reactions which are primarily involved in oxidative reactions (Matkowski *et al.,* 2013) [6].

Anti-inflammatory effects of mangiferin

Mangiferin is a well-known anti-inflammatory (Leiro *et al*., 2004) [24] substance and an efficient antioxidant (Andreu *et al*., 2005) [25]. It modulates inflammation mostly by modulation of two pathways, namely NFkB pathway and PARP-Gamma pathways.

Ample of studies have revealed the fact Mangiferin dampen downs the inflammatory response basically by interference with Nuclear Factor κ-light-chain-enhancer of activated B cells (NFκB) (Dou *et al.,* 2014) [26]. Mangiferin disrupts various phases in the conventional or alternative NF-kB activation pathways. The IKKa inhibitors and p52 regulate the alternative pathway, whereas the IKKa complex and p50 regulate the conventional pathway. Mangiferin also blocks TNFR1—Tumor Necrosis Factor Receptor type-1-Associated Death Domain protein (TRADD), TNFR-Associated Factor 2 (TRAF2), factors of NCK Interacting Kinase (NIK), and IKK that promote the expression of Secreted Embryonic Alkaline Phosphatase (SEAP). However, there is no discernible impact on p65, which is in charge of SEAP expression. Mangiferin also suppresses MAPKs p38, which are controlled by an external signal (ERK) and kinase phosphorylation at the c Jun N terminus (Jeong *et al*., 2014) [27], decreasing the MAPK signal (Dou *et al*., 2014) [26].

Inflammatory response of mangiferin can also be attributed to the PARP-Gamma (Peroxisome Proliferator-Activated Receptor Gamma) pathway. Due to binding of corresponding ligand to PARP-Gamma, transcriptional activities work in various ways to suppress COX-2, (Vandoros *et al*., 2006) [28]which plays s central role in the process of inflammation by triggering release of modulators of inflammation known as prostaglandins (Hugo *et al*., 2015) [29]. Mangiferin increases the mRNA expression of PARP-gamma by several folds leading to decreased transcriptional activity of COX-2. This suppresses inflammation and makes the environment less conducivefor the malignant cells to proliferate (Mahmoud-Awny *et al*., 2015) [30]. Mangiferin also suppresses the activity of COX-2 via TGF-Beta (up regulation) and NFkB (down regulation) pathways (Garcia-Riveria *et al.,* 2011) [31]. Mangiferin may be helpful in modifying the regulation of PPAR gamma as well as COX-2, according to *in vitro* research on the MDA-MB-231cells (Telang *et al*., 2013) [32].

Anti-oxidant activity of mangiferin

Fall out of oxidative stress is due to the failure of antioxidants and detoxification systems to function properly in balancing the burden of ROS (Reactive Oxygen Species). Too many ROS can hamper cellular activity by causing damage to DNA, lipids and protein.Reactive oxygen species (ROS), which produce inflammation, are the first significant factor (Naik *et al*., 2011) [33]. Oxidative stress can be seen as an important factors that aggrevates cancer. Agents bearing antioxidant properties have caught the clairvoyant eyes of imminent researchers (Nersesyan *et al.,* 2007) [34]. Magniferin is one such wonder. (Mangiferin works well as a ROS scavenger (Leiro *et al.,* 2003) [24]. Mangiferin (1, 10, 100 g/mL) has been found to improve red blood cells' resilience to hydrogen peroxide-induced ROS (Rodríguez *et al*., 2006) [35]. Mangiferin scavange Reactive oxygen species by three pathways, i.e., modulating the Nrf2/antioxidant response element (ARE) detoxification pathway, directly detoxifying reactive species and activating detoxification enzymes such as catalase.

Nrf2 accumulates in nucleus and form heterodimers with musculo aponeurotic fibroma (maf) protein (Zhao *et al*., 2014) [36]. This triggers initiation of transcription of number of phase 2 detoxification system NADPH, quinine reductase (NQO1), glutathione-S-transferase and heme oxygenase system (HQ-1) (Zhang *et al.,* 2015; Zhao *et al*., 2014) [37, 36]. Mangeferin interferes with the Nrf2/ARE pathways in many steps (Zhang *et al*., 2014; Zhang *et al.,* 2015; Zhao *et al*., 2014) [38, 37, 36]. It increases the accumulation of Nrf2 in nucleus in a time dependent manner and helps in detoxification process (Zhang *et al*., 2015) [37]. Mangiferin can very well differentiate between the healthy cells (human umbilical cord mononuclear blood cells) and malignant cells (HL-60) and promotes Nrf2/ARE activity in healthy cells only, which make it a promising anti-cancer agent (Zhang *et al*., 2014) [38].

Both *in vitro* and *in vivo*, it up regulates expression of various detoxifying agents and thus enhancing the clearance of ROS from body. It can restore glutathione activity and reduces action of superoxide (Kavitha *et al.,* 2013) [5]. Mangiferin tends to increases GSH levels in body by causing up-regulation of Gamma-Glutamyl cysteine Synthetase, an enzymes that regulates the much important rare limiting step of Glutathione synthesis, further revealed that mangiferin's ability to minimise oxidative stress can be linked to its NFkB down-regulating capabilities leading to reduced TNF-induced reactive oxygen intermediate generation (Sarkar *et al*., 2004) [39].

Catalase is a known detoxification enzyme which can converts Hydrogen peroxide into water and oxygen. It is present in most of the organisms present in the Earth. H2O2 can induce cell damage if not promptly converted into less toxic species. Magnefiren has shown to directly interact with catalase and thereby reducing the tissue damage so caused to a great extent. Sahoo *et al*. has demonstrated that binding of mangiferin to catalase increased is activity by 44% *in vitro* (Sahoo *et al.,* 2015) [40].

Thus, anti-oxidant activity of mangeferin has been established through various studies which elucidate its tissue protective property that attributes to its anti-inflammatory and anti-

cancerous behaviour. Mangiferin at the concentration of 1, 10 and 100 mg/mL is shown to increase the resistance of the red blood cells to the hydrogen peroxide induced Reactive Oxygen Species (ROS) (Rodriguez *et al*., 2006) [35].

Anti-cancer effects of mangiferin

Cancer is leading cause of non-communicable disease mortality (WHO, 2015) [41]. There are six hallmarks of neoplasm and these include uncontrollable growth, immortality and the ability to invade other tissues. Cancerous cells undergo unregulated growth and have the ability to metastatise to other parts of the body via lymphatic system. It interferes with the apoptotic pathways in a way to evade it and induce uncontrolled growth (Mantovani, 2009) [42]. Under normal fabric, apoptosis is induced either by the intrinsic pathway via the mitochondria, or the extrinsic pathway involving death receptors (Kim *et al*., 2012) [43].

In both *in vitro* and *in vivo* settings, there is a tonne of data for mangiferin's anti-cancer effectiveness against a variety of malignant tumours. Mangiferin uses a number of ways to carry out this function. Mangiferin acts in different ways depending on the type of cancer cell and its growth pathways. Mangiferin can block, stabilise, or activate particular enzymes or proteins, merely alter the signalling of transcription factors, or it can protect DNA from damage. When these actions are carried out simultaneously, mangiferin is able to readily interrupt the cell cycle, which encourages the apoptosis of many cancer types. Additionally, it can enhance the effects of other cancer medications by increasing their efficacy against chemotherapy-resistant tumours. (Morozkina*et al*., 2021) [23].

DNA damage facilitates mutation which is the prime requirement for cancer to initiate and develop. Higher DNA damage increases the susceptibility to cancer (Valko *et al*., 2004) [44]. Mangiferin has the ability to protect not only DNA (Zhang *et al*., 2014) [38] but deoxyribose, phospholipids, polyunsaturated fatty acids and proteins (Matkowski *et al*., 2013) [6]. Studies have revealed that mangiferin and mangiferin aglycone offer protection against radiation damage *in vitro*. Lei *et al*. showed that pre-treatment of human intestinal epithelial cells with mangiferin aglycone reduced the double strand breakages in their DNA by 47% (Lei *et al*., 2012) [45].

In neoplasm, there is aberrant activation of Beta-catenin. Mangiferin acts in a way to suppress Beta-catenin pathways (Li *et al*., 2013) [46]. Also, Mangiferin is known to attenuate Mitogen Activated Protein Kinase Pathway (MAPK) by signalling the inhibition of MAPKs p38, Extracellular signal-Regulated Kinase (ERK) and cJun N-terminal Kinase phosphorylation (Dou *et al*., 2014; Zhang *et al*., 2014) [26, 38]. MAPK is believed to play a pivotal role in tumorogenesis pertaining to cell proliferation, growth, differentiation and migration (Santarpia *et al*., 2012) [47]. Mangiferin is beileved to induce G2/M phase arrest,which is responsible for cell growth progression (Lv *et al*., 2013) [1].

Normally, the rate of cell death and cell replication is balanced in order to maintain hoemostasis. In cancerous cell, this balance is shifted towards cell replication leading to uncontrolled growth of cells. Studies have established that mangiferin reduces cell proliferation by modulating beta-catenin, and thus metalloproteinase-7 (MMP-7), metalloproteinase-9 (MMP-9) and epithelial to mesenchymal transition (EMT) (Li *et al*., 2013; Xiao *et al*., 2015) [46, 48]. In numerous breast cancer cell lines, mangiferin has been shown reduced cell proliferation (MDA-MB-231, BT-549, MCF-7 and T47D) and metastasis (MDA-MB-231 and BT-549)in a dose-dependent manner (Lv *et al*., 2013; Li *et al*., 2013) [1, 46].Li *et al*. re-established in HL-60 cell line that mangiferin reduces cell proliferation (Li *et al*., 2013) [46].

In cell lines IRB3 AN27 (a type of nerve cell from the human foetus), HeLa (cervical cancer), MCF-7 (breast cancer), and U-937 (lymphoma), ROS inhibitors have been found to stimulate NF- kB (Nuclear Factor k-light-chain enhancer of activated B cells) (Sarkar *et al*., 2004) [39]. Mangiferin (10 g/mL) suppresses IRAK1 phosphorylation in peritoneal macrophages, which prevents NF-kB expression that is brought on by lipopolysaccharides (LPS) and peptidoglycan (PDG) from being activated (Jeong *et al*., 2014) [25]. Additionally, mangiferin inhibits NF-kB activation via inflammatory genes (du Plessis-Stoman *et al*., 2011) [49].

Mangiferin also plays a significant role in dwindling metastatic process of cancer spreading. Activation of matrix MMPs is a vital step in metastasis because enzymes facilitate cell to escape from the initial site of the malignancy, by degrading the extracellular matrix. Li *et al*. have demonstrated that it can interfere with MMP pathways leading to reduced metastasis (Li *et al*., 2013) [46]. Dilshara *et al*. has demonstrated that in LNCaP prostate cancer cells, activation of NFkB by TNF-alpha increases the levels of MMP-9 mRNA and protein present in the cell, Mangiferin is capable of attenuating this effect, ultimately reducing metastasis (Dilshara *et al*., 2015) [50].

Polyphenols like mangiferin have the ability to hinder the onset of lipid peroxidation and thereby icreasing the serum antioxidant activity, which accounts for its chemotherapeutic actions (Zasada *et al*., 2011) [51]. Mangiferin induces loss of mitochondrial membrane potential and thus can activate apoptotic process (Kavitha *et al*., 2013) [5].

Mangiferin has shown its activity against breast cancer, triple negative breast cancer, lymphoma, cervical cancer, mouse melanoma, acute myeloid leukemia, glioma, prostate cancer, hepatocellular carcinoma, lung carcinoma and colon cancer. The anti-cancer activity of mangiferin against breast cancer is due to activation of NFkB, inhibition of P-gp activity, downregulation of CDK1- cyclin B1 signaling pathway, induction of G2/M phase cell cycle arrest, increasing caspase-3, caspase-8 and caspase-9 activity and decreasing expression of procaspase-3, procaspase-8 and procaspase-9 (Sarkar *et al*., 2004; Sahoo *et al*., 2015; Loisa *et al*., 2014; Lv *et al*., 2013) [39, 40, 52, 1]. The activity of mangiferin against triple negative breast cancer is due to the induction of decreased expression of MMP-7, MMP-9 and EMT, inhibition of beta-catenin pathway, decreased tumour volume, weight and proliferation, increased apoptosis, lowered expression of MMP-7, MMP-9, vimentin, activation of beta-catenin and increased expression of E-cadherin (Li *et al*., 2013) [46]. The activity of mangiferin against lymphoma is due to activation of NFkB (Sarkar *et al*., 2004; Sahoo *et al*., 2015) [39, 40]. The activity of mangiferin against cervical cancer is due to activation of NFkB, downregulation of BH3, Bcl-2, procaspase-3 and procaspase-8, increased activation of caspase-3, caspase-7, caspase-8 and caspase-9 and induction of delay in the S-phase (Kim *et al*., 2012; du Plessis *et al*., 2011) [43, 49]. The activity of mangiferin against mouse melanoma is due to suppression of nuclear translocation of NFkB, decreased expression of phosphorylated NIK, IKK, IkB, inhibited expression of MMP-1, MMP-2, MMP-9, MMP-14, VLA-4, VLA-5 and VLA-6, enhanced expression of cleaved caspase-3, cleaved PARP-1, p53 proteins, reduced expression of Survinin and

Bcl-xL (Takeda *et al*., 2016) [53]. The activity of mangiferin against acute myeloid leukemia is due to activation of G2/M phase cell cycle arrest by modulating CDK-1 cyclin B1 signalling pathways, induction of Wee 1 mRNA expression of Chk 1 and cdc25C, inhibition of phosphorylation of Ataxia Telangiectasia and Rad3- related protein (ATR), Chk 1, Wee 1, Akt and Erk ½, decreased activation of cyclin B1, enhanced Nrf2 binding of antioxidant response element (ARE), modulation of of NQO1 expr-ession, restriction of intracellular ROS levels, reducing the nuclear penetration of NFkB p65, blocking the expression of Bcl-xL and XIAP (Zhao *et al*., 2014; Zhang *et al.*, 2014) [36, 38]. The activity of mangiferin against glioma is due to promotion of miR–15b and inhibition of MMP-7, MMP-9 and EMT (Jung *et al*., 2012) [54]. The activity of mangiferin against prostate cancer is due to reduction of TNF-α induced MMP-9 activity relieving of NFkB activity, inhibition of nuclear translocation of the NFkB subunits p65 and p50 (Dilshara *et al.*, 2015) [50]. The activity of mangiferin against hepatocellular carcinoma is due to enhanced expression of CDC2 and ccnb1 mRNA, β-catenin independent Wnt pathway, downregulation of MYC, axin2, MMP-2 and CCND1 and decreasing AST, ALT, ALP and LDH levels (Yao *et al*., 2010; Huang *et al*.,2002; Yang *et al*., 2019; Tan *et al*., 2018) [55-58]. The activity of mangiferin against lung carcinoma is due to induction of G2/m phase cell cycle arrest through the CDK-1 cyclin B1 signaling pathway, inhibition of PKC-NFkB pathway, increased levels of glutathione catalase (CAT), superoxide dismutase, glutathione reductase, glutathione peroxidise, Vitamin C and vitamin E, enhanced lipid peroxidation, decreased activity of catalase and superoxide dismutase, decreased activities of GST, quinine reductase (QR) and uridin 5'-diposphate – glucoronosyl transferase (UDP-GT), decreased levels of polyamines, protein carbonyl, nucleic acid content and lipid peroxidation, decreased lysosomal enzymes β-glucuronidase, acidophosphatase, β-galactosidase and N-acetyl glucosaminidase (Cheng *et al*., 2007; Rajendran *et al*., 2008; Rajendran *et al*., 2014) [58, 60, 61]. The activity of mangeiferin against colon cancer is due to reduction of NFkB activation, increase in delay in the S phase, increase Nrf2 and magnesium superoxide dismutase (MnSOD) (Yoshimi *et al*., 2001)[62].

Mangiferin has the ability to negate the side effects caused by chemotherapeutic agents by selectively targeting malignant cells for cell death and letting the healthy cells survive normally. It can potentiate cell death of malignant cells by modulating NfkB pathways (Sarkar *et al*., 2004) [39].

Characteristics of Mangifein according to various studies

1. Mangiferin combines well with hydrophilic polymers having smaller molecular sizes than hydrophobic polymers or bulky molecules
2. Mangiferin can closely combine with polymers bearing positive charge (for e.g., chitosan) and paves the way for development of a sustainable polymer system. However, it renders the release of drug difficult. Elaborate research is required to have an appropriate ratio while combing the polymers with mangiferin.
3. Mangiferin loading polymer systems form both inter-molecular and intra-molecular hydrogen.
4. Mangiferin has the capacity to bind to the hydrophilic and hydrophobic parts of polymer system, which increases the encapsulation efficiency, loading efficiency, solubility and permeability by several folds.
5. Maximum polymer systems of mangiferin dissolve better in acidic medium than in basic medium and the solubility can be adjusted by making changes in the proportion of the polymers in the system.
6. Generally, the size of the system increases with increasing proportion and molecular sizes of the polymers.
7. The surfactant chemical structure influences the characteristics of mangiferin-polymer systems including its particle size, distribution of mangiferin and active ingredients in the matrix or their total properties. The release of active ingredients from the polymer systems is accelerated due to presence of surfactants. (Morozkina *et al*., 2021) [23].

Conclusion

Mangiferin has been shown in multiple studies to have a wide range of biological effects, including its methods of anti-cancer action against various malignancies. But its poor oral bioavailability and poor body absorption limit its therapeutic application. According to this perspective, there is a pressing need for research into new mangiferin drug delivery systems.Mangiferin is comparable to a priceless gift from nature that we were unaware of for a very long time because its many qualities have just recently been investigated. It is necessary to conduct additional research on the maintenance, enhancement, and extension of the excellent biological activity of mangiferin in polymer systems, including Mangiferin can be considered as a wonder in field of anti-cancer research that have shown therapeutic effect against multitude of ailments including cancer. This has great potential for further research in order to bring it to the fore foot of anti-cancerous agent being used in clinical practice.

There is immense scope for creating new polymer systems with higher encapsulation quality, better drug loading, and biological effects, using in other different encapsulation techniques, implementing more thorough encapsulation techniques and conducting additional *in vitro* and *in vivo* studies with the goal of using these advancements to treat life-threatening diseases in people (Morozkina*et al*., 2021) [23].

Abbreviations

1. ALP- Alkaline phosphatise
2. AML-Acute myeloid leukemia
3. ARE – Antioxidant response element
4. AST – Aspartate Aminotransferase
5. ATR – Ataxia Telangiectasia and Rad3- related protein
6. Bax – Bcl-2 associated X protein
7. Bcl-2 – B Cell Lymphoma 2
8. Bcl-xL – B Cell Lymphoma- extra large
9. Chk 1 - Checkpoint Kinase 1
10. CDK1 – Cyclin-Dependent Kinase 1
11. COX-2 Cyclooxygenase-2
12. DEN – diethylnitrosamine
13. ERK- Extracellular Regulated Kinase
14. GSH – Glutathione-S-transferase
15. JNK – c-Jun terminal kinase
16. IKK- alpha – Inhibitor of NFkB Kinase subunit-alpha
17. IKK-beta – Inhibitor of NFkB Kinase subunit-beta
18. IL-1R – Interleukin-1 Receptors
19. IL-6 – Interleukin-6
20. IL-8 – Interleukin-8
21. IRAK1 – Interleukin-1 Receptor Activated Kinase 1
22. LEFI – Lymphoid Enhancer Binding Factor 1

23. MAPK- Mitogen Activated Protein Kinase
24. MMP – Matrix metalloproteinase
25. MYC – MYC Proto-Oncogene, BHLH Transcription Factor
26. NFkB–Nuclear Factor k- light chain-enhancer of activated B cells
27. NIK – NCK Interacting Kinase
28. NQO1 – NAD(P)H: quinine reductase
29. Nrf2 – Nuclear factor erythroid 2-Related Factor 2
30. PARP – Poly ADP ribosepolymerase 1
31. PDG – Peptidoglycan
32. PKC – Protein Kinase C
33. PPAR – Peroxisome Proliferator Activated Receptor Gamma
34. QR- Quinone Reductase
35. ROS- Reactive Oxygen Species
36. SEAP – Secreted Embryonic Alkaline Phosphatase
37. TNF – Tumor Necrosis Factor Receptor
38. TRADD – TNFR with Tumor Necrosis Factor type-1-Associated death Domain Protein
39. VEGF – Vascular Endothelial Growth Factor
40. XIAP – X linked Inhibitor of Apoptosis Protein

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