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REVIEW

Pharmacological Activity and Mechanism of Tanshinone IIA in Related Diseases

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Salvia miltiorrhiza: (Danshen) is a significant (traditional Chinese medication) natural remedy, enhancing blood circulation and clear blood stasis. In this view, it is widely used against several heart diseases, eg, cardiomyopathy, arrhythmia, and congenital heart defects. Tanshinone IIA (tan-IIA) is the main fat-soluble component of *Salvia miltiorrhiza*. Modern pharmacological study shows that tan-IIA has anti-inflammatory and anti-oxidant activities. Tan-IIA induces remarkable cardioprotective effects via enhancing angiogenesis which may serve as an effective treatment against cardiovascular diseases (CVD). There is also evidence that tan-IIA has extensive immunomodulatory effects and plays a significant role in the development and function of immune cells. Tan-IIA reduces the production of inflammatory mediators and restores abnormal signaling pathways via regulating the function and activation of immune cells. It can also regulate signal transduction pathways, ie, TLR/NF-κB pathway and MAPKs/NF-κB pathway, thereby tan-IIA has an anti-inflammatory, anticoagulant, antithrombotic and neuroprotective role. It plays a protective role in the pathogenesis of cardiovascular disorders (ie, atherosclerosis, hypertension) and Alzheimer's disease. It has also been revealed that tan-IIA has an anti-tumor role by killing various tumor cells, inducing differentiation and apoptosis, and has potential activity against carcinoma progression. In the review of this fact, the tan-IIA role in different diseases and its mechanism have been summarized while its clinical applications are also explored to provide a new perspective of *Salvia miltiorrhiza*. An extensive study on the mechanism of action of tan-IIA is of great significance for the effective use of Chinese herbal medicine and the promotion of its status and influence on the world.

Keywords: tanshinone-IIA, atherosclerosis, Alzheimer' disease, cancer, anti-inflammation, anti-oxidative

Introduction

Salvia miltiorrhiza (named Danshen in Chinese) is a Chinese herbal remedy, also known as Chinese sage, composed of dried rhizomes and roots of *Salvia miltiorrhiza* Bge[1] which was first published in *Shennong Bencaojing*. It has the effects of relieving pain, promoting blood circulation, and removing blood stasis.[2] Modern pharmacological research has found that *Salvia miltiorrhiza* has dilated coronary artery,[3] prevents myocardial ischemia,[4] myocardial infarction[5] improves microcirculation,[6] and reducing myocardial oxygen consumption.[7] In Asian countries, for hundreds of years, *Salvia miltiorrhiza* is widely used against various heart complications.[8] A large number of experimental and clinical studies have reported that *Salvia miltiorrhiza*, whether it is the original drug or prepared (Danshen injection),[9] Danshen dropping pills, Danhong injection and Danshen Gegen soup

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are beneficial to the heart during pathological processes, such as myocardial ischemia,[10] myocardial infarction, reperfusion injury[11] and so on.

Research on the chemical constituents of *Salvia miltiorrhiza* has been in place since the 1930s.[12] Since then, many researchers have focused on separating and identifying components from this plant. At present, more than 200 compounds have been identified from *Salvia miltiorrhiza* Bge,[13] according to the Chinese Academy of Sciences Chemical Database (www.organchem.csdb.cn) and the Chinese herbal medicine database.[14] Tan-IIA is a representative of the fat-soluble[15] component of *Salvia miltiorrhiza* (as shown in Figure 1), and other tanshinones and the hydrophilic component of *Salvia miltiorrhiza* (salvianolic acids) also play important roles in the pharmacological activities of danshen in treating various diseases. The terpenoids are easily reduced to diphenol derivatives,[16] which are then oxidized[17] and easily converted.[18] Quinone compounds play a role in the transmission of electrons,[19] as a product of metabolism of organisms,[20,21] exhibits a variety of biological activities by promoting or interfering with various biochemical reactions of organisms,[22] and promotes certain biochemical reactions as coenzymes[23] for biological reactions.[22] Or interfere with the action,[24] thus showing a variety of pharmacological effects, such as anti-atherosclerosis,[25] anti-myocardial ischemia,[26] anti-arrhythmia,[27] repair of vascular endothelial cells,[28] improve coronary blood circulation,[29] anti-cardiac hypertrophy, and anti-tumor (as shown in Figure 2).

Over the past few years, the compounds (particularly tan-IIA) isolated from the *Salvia miltiorrhiza* have been evaluated for their biological activities. Numerous proposed mechanisms have been reported on the role of tan-IIA in cardiovascular protection, including apoptosis and autophagy, anti-inflammatory,[30] antioxidant, antithrombotic, anti-proliferation[31] of vascular smooth muscle cells, inhibition of expression of vascular endothelium[32] and leukocyte adhesion molecules,[33] and improve acute myocardial ischemia.[33] At the same time, studies have found that tan-IIA has a significant contribution to the activation, development, and proper functioning of immune cells. Tan-IIA is involved in both the innate and the acquired immune response which facilitates all stages of inflammatory pathways (from initiation to progression). Despite the in-depth study of the pharmacological effects of tan-IIA on cardiovascular system in-vitro, in-vivo, and clinical trials, its mechanistic target is remaining elusive. This article briefly reviews the research status of the pharmacological effects of tan-IIA in cardiovascular diseases and provides a reference for clinical rational drug use.

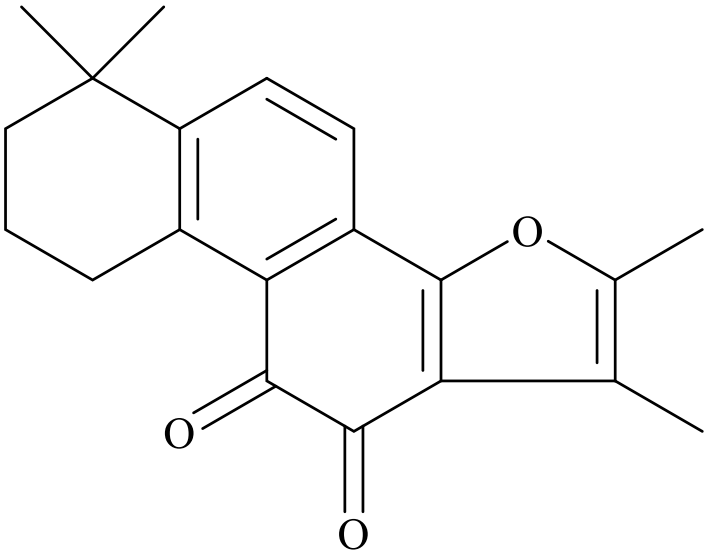

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Figure 1 The chemical structures of the major lipophilic components (tanshinone-IIA) are shown in A.

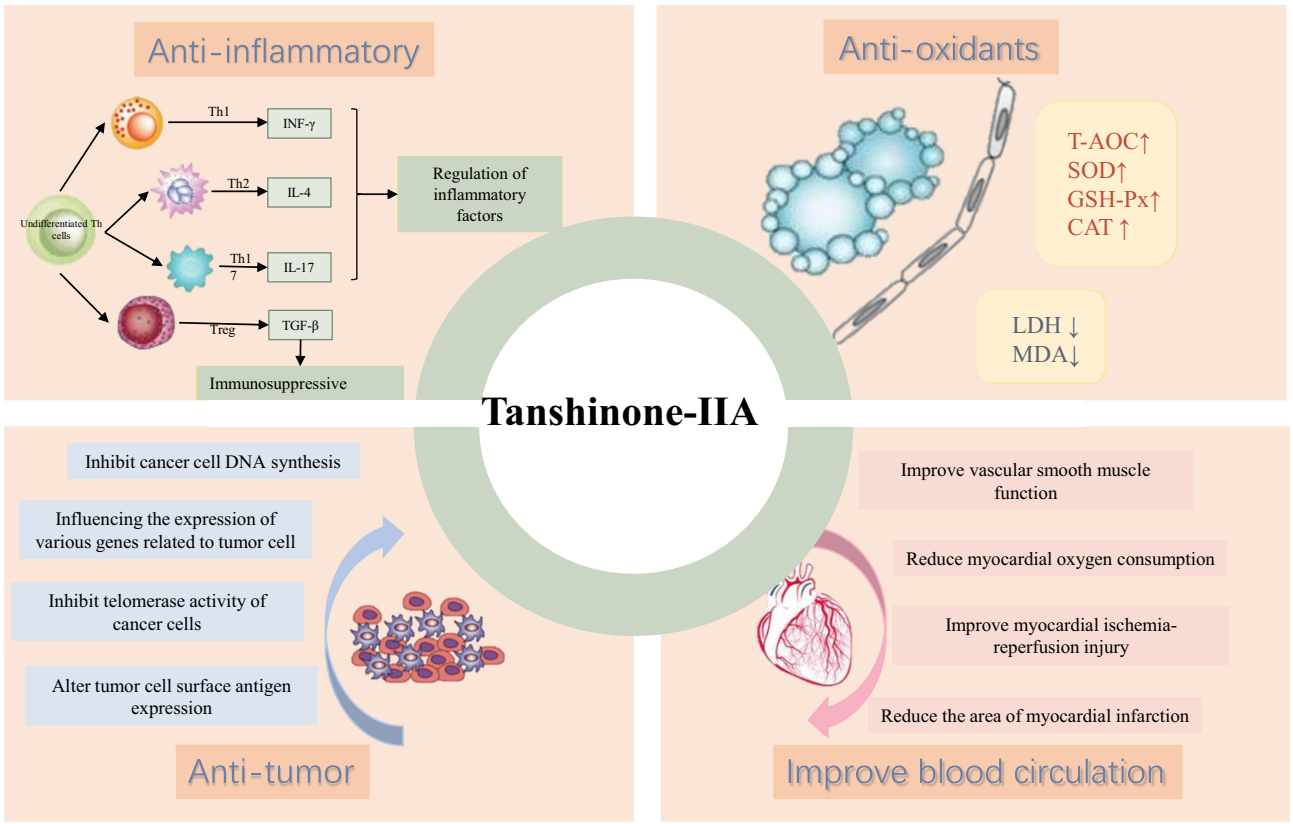

Figure 2 Pharmacological activity And effects of tanshinone-IIA.

Tanshinone IIA Has a Significant Contribution to the Development, Activation, and Function of Immune Cells

Function and Activation of Immune Cells

Dendritic Cells

Dendritic cells (DC) are the largest antigen-presenting cells (APC) in the body. These cells induce the innate immune responses via presenting antigens to thymus-dependent lymphocytes (T cells).[34] During the up-regulation of antigen-presenting molecules (ie, MHCI, MHC II, and CD1), CAMs (cellular adhesion molecules ie, CD54, CD58, CD11a/CD18, and CD50) and costimulatory molecules (ie, CD40, CD80, and CD86),[35] due to endocytosis and antigen processing along with the weakening capacity, DC gradually matures, and then the ability of antigen presentation to T cells is significantly enhanced. Therefore, tan-IIA weakens the developmental process of immune system disorders by inhibiting the adaptive immunity, mediated by dendritic cells. A study confirms that tan-IIA has the potency to enhance the CD4(+) T cells polarization into Treg cells via DCs targeting to induce the upregulation of TGF-β1 (transforming growth factor β1) as well as via in-vitro naïve CD4(+) T cells direct targeting. Additionally, tan-IIA has a considerable role against neuroinflammation and may serve as a candidate therapeutic approach to cure the neuroinflammatory disorders eg, optic neuritis, transverse myelitis, and neuromyelitis optica.[36] Li et al reported that tan-IIA attenuated CD86 expression on DC, reduced CD54 and MHC II expression level, recovered the capacity for endocytosis, and overcome the inflammatory cytokines (eg, IL-12 and IL-1) secretion as well in dose-dependent manner.[37] Because of the underlined significant activities of tan-IIA, it may serve as an effective therapeutic approach against the progression of the atherosclerotic lesion.

T Lymphocytes or T Cells

T lymphocytes or T cells consider the principal lymphocytes components, associated with a variety of biological responses eg, inhibiting B cells from antibodies production, cytokines production, target cell killing, and specific response to mitogens and antigens.[38] Cellular immunity is dependent on T cells immune response production.

Cellular immunity is comprised of two types: specific binding and destructing the plasma membrane of target cells via forming a transmembrane pore, and direct killing of target cells.[39] Most of the activated CD4(+) T cells can stimulate the aggregation of cytokines, and secrete the IL-12, IFN-γ (interferon-γ) and other pro-inflammatory cytokines that ultimately resulting in inflammation.[40] According to the reported studies,[41] tan-IIA elevates the level of anti-inflammatory cytokines, such as IL-10, while decreases the level of inflammatory cytokines, such as IL-2, IL-4. It has also been reported that tan-IIA elevates the level of T cell subsets such as CD3(+), CD4(+), and CD8 (+). In view of this fact, tan-IIA may work as a lead compound for the development of effective medical treatment against liver laceration (liver injury). Yan et al studied[42] that tan-IIA is associated with the downregulation of serum and brain IL-17 and IL-23 in the experimental autoimmune encephalomyelitis (EAE) rats. They also studied that this compound can lower the amount of CD4(+) T cells, CD8(+) T cells, and microglia and macrophages in the spinal cord. Their results confirm that tan-IIA relieves EAE and supports its use as a new treatment for multiple sclerosis.

Production of Cytokines

Cytokines (CK) are low-molecular-weight soluble proteins that are induced by immunogens, mitogens, or other stimulants to produce a variety of cell features.[43] In the development of inflammation, cytokines show a very important role, mainly the relationship between pro-inflammatory and anti-inflammatory cytokines[44] that promote each other and restrict each other. The dynamic changes of the two cytokines determine the development and outcomes of inflammation. A pleiotropic cytokine ie, IL-6 has dual effects of pro-inflammatory as well as anti-inflammatory effects.[45] A reported study[46] demonstrated that in the streptozotocin (STZ) rat model of DPNP, tan-IIA had efficient antihyperalgesic and antiallodynic abilities. This compound elevated the level of IL-10 (a cytokine with potent anti-inflammatory efficiency) and had an inhibitory potential against proinflammatory cytokines such as IL-1β, IL-6, and TNF-α. Based on these remarkable effects, tan-IIA might be used as a leading anti-inflammatory drug. IL-8 and monocyte chemoattractant protein 1 (MCP-1) are chemokines that induce monocyte adhesion to endothelial cells. IL-8 may attract T cells and cause smooth muscle cell (SMC) proliferation and migration. At the same time, MCP-1 can stimulate local infiltration, aggregation, and monocytes/macrophages proliferation.[47]

The data revealed that the tan-IIA analgesic effects in neuropathic pain are mostly activated by down-regulating SNL-induced astrocytic activation through blockage of JNK/MCP-1 cascade. MMP activation causes degradation of the extracellular matrix which results in the disruption of the fibrous cap and finally leads to the instability and rupturing of plaque. Among the subtypes of collagenases, type-IV collagenases, such as MMP-2 and MMP-9[48] have a role in local inflammatory cell infiltration in plaques. In plaques, the cell's infiltration is the important element that causes injury to the walls of blood vessels and reduced the intima defense functions. Based on the results of Zhou et al, tan-IIA can decrease the expression level of MMP-9 and MMP-2 and inhibit the expression of p50 and p65. So, the migration and invasive ability of HNE-1NPC cells are blocked via tan-IIA by decreasing the expression level of matrix metalloproteinase.

Inflammation-Related Signal Transduction Pathway

Toll-Like Receptor/NF-κB Pathway

The Toll-like receptor (TLR) family is the main receptor for host cells to recognize various microbial pathogenic components. NF-κB is situated at the hub of the downstream signaling cascade of TLR. When biological stress activates cells, as a result, NF-κB is stimulated which translocates into the nucleus. In the nucleus, it regulates the expression level of inflammatory cytokines such as MCP, and cell adhesion molecules eg, ICAM-1and VCAM-1, and also initiate innate and acquired immune responses against pathogenic microbes[47,49] (Figure 3). The downstream signaling pathways of TNF-α and TLR4/NF-κB are critical for the inflammatory signaling cascades.[50] The TNF-α is an inflammatory cytokine and its expression level reflects the pathogenesis and severity of the inflammatory process. According to Meng et al,[51] in-vitro study, in VSMCs, LPS-induced inflammatory responses were found to be inhibited via tan-IIA by partially suppressed TLR4/TAK1/NF-κB signaling cascade. The results showed that by using tan-IIA, the neuronal TLR-4 and NF-κB expression levels were found to be reduced, while inflammatory cytokines production and neuronal oxidative stress levels were found to be elevated.[52] Given these results, tan-IIA is a significant approach for enhancing HIE through NF-κB signaling mediated via TLR-4. Du

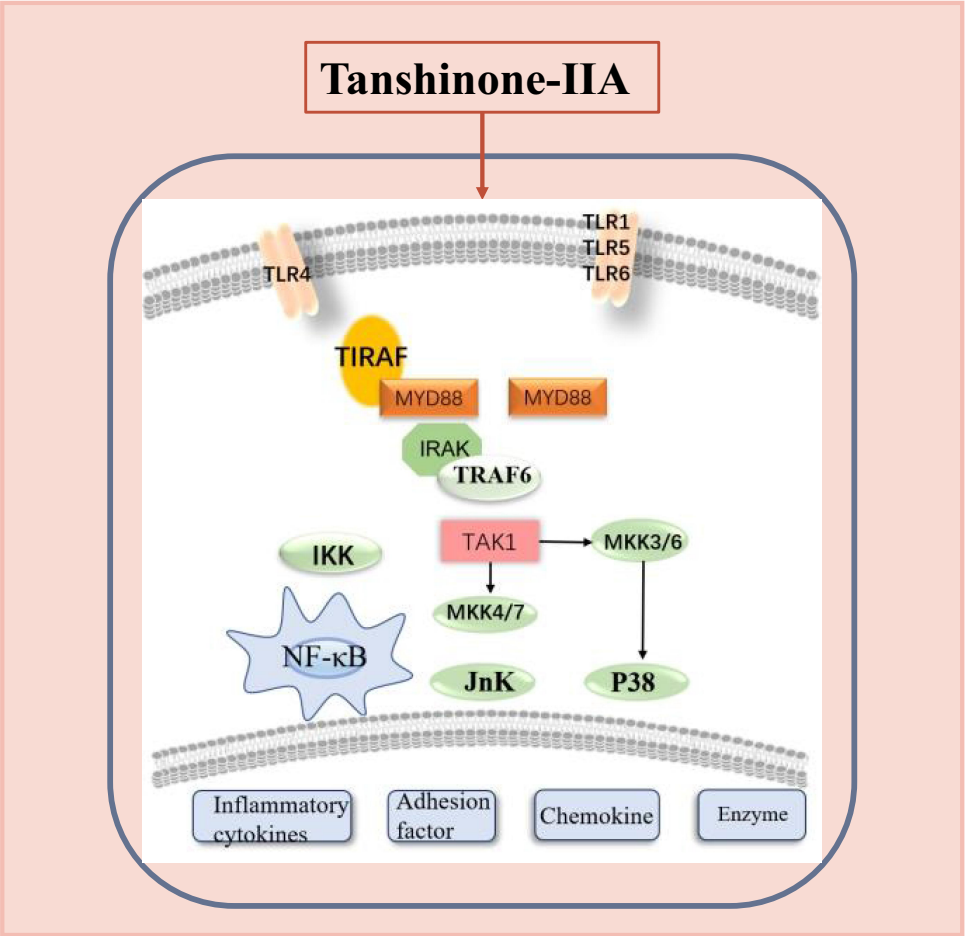

Figure 3 NF-κB inflammation signaling pathway diagram.

et al also revealed[53] that this compound remarkably suppressed the enhanced transcriptional level of some matrix metalloproteinases and proinflammatory factors activated via TNF-α in RA-FLSs, which prevent the inflammatory reactivity, leading to prevent the knee joint disruption.

Mitogen-Activated Protein Kinase Pathway

Mitogen-activated protein kinases (MAPKs) are a class of Ser/Thr protein kinases in cells that contribute to various biological and physiological behavioral processes of cells, including gene transcription, cell differentiation and proliferation, cell cycle regulation, apoptosis, and inflammatory reactions.[54] MAPKs comprise three well-characterized subfamilies ie, extracellular regulated protein kinase (ERK), c-Jun N-terminal protein kinase (JNK), and p38 MAPKs.[55] The ERKs are one of the key signaling cassettes, have a significant contribution to cellular growth, development, and differentiation, while JNK and p38 both have a key role in cellular apoptosis. Li et al studied[55] that tan-IIA has an inhibitory activity against glutamate-induced apoptosis via regulating the expression of proteins vital to cellular apoptosis and MAPK activation, including the overexpression of Bcl-2 protein, reduced level of Bax and cleaved caspase-3, and suppression of JNK and p38 MAPK activation. Fang et al results[56] indicated that tan-IIA hinders the THP1 cells adhesion to activated-endothelial cells which are activated via TNF-α. Moreover, a mechanistic study illustrates the correlation of p38 MAPK/NF-κB cascade with tan-IIA mediated pharmacological effects.

Pharmacological Effects of Tanshinone-IIA in Diseases

Atherosclerosis

Worldwide, atherosclerosis and subsequent cardiovascular diseases cause millions of deaths each year. Atherosclerosis is a multi-arterial inflammatory disease[57] characterized by oxidative stress, inflammatory responses,

and immune disorders.[58] This is a condition in which the arteries are narrowed and the elasticity of the arterial wall is lost due to excessive accumulation of viscous plaque in the intima of the arteries.[59] The mechanism of atherosclerosis is associated with the destruction of lipoprotein metabolism and inflammation and has become the main focus of atherosclerosis research.[60] Previous studies have found that in atherosclerosis, tan-IIA acts by inhibiting low density lipoprotein (LDL) oxidation,[61] migration and development of smooth muscle cells, monocytes adhesion to the arterial endothelium, expression of pro-inflammatory cytokines, aggregation of platelets[62] and cholesterol accumulation mediated by macrophages.[63] However, current treatments for the inflammatory properties of atherosclerosis are still very limited. The tan-IIA cardioprotective effects are mainly associated with its anti-inflammatory and antioxidant activities. Tan-IIA has some potential to stabilize plaques in atherosclerosis. This section describes the protective effect of tan-IIA in atherosclerosis and its mechanism of action providing a new perspective for the clinical application of tan-IIA.

Anti-Inflammation

The inflammatory reaction has a key contribution to the occurrence as well as the development of diseases. Inflammation is a key factor in the development of atherosclerosis.[63] Over time, many anti-inflammatory strategies have become potential treatments for atherosclerotic disease.[64] Lipopolysaccharide (LPS) is the main constituent of the gram-negative bacterial cell wall and is responsible for the inflammatory response in animals as well as in humans. LPS transmits signals into cells through its receptor TLR4 and stimulates the nuclear factor NF-κB which can induce the expression of a series of inflammatory genes, leading to the release of a variety of inflammatory mediators and cytokines, which ultimately causes local or systemic inflammatory response syndrome. Therefore, by effectively blocking the abnormal activation of NF-κB may become an effective way of clinical anti-inflammatory target. Tan-IIA reduces atherosclerosis by inhibiting the inflammatory response.

Chang et al study showed that tan-IIA dose-dependently blocked the adhesion of human vascular endothelial cells by reducing IKK/NF-κB signaling cascade activation and further attenuates the expression of VCAM-1, ICAM-1, and fractalkine.[65] According to Wang et al, tan-IIA suppressed the development of atherosclerosis through inhibition of vascular inflammation, VSMCs apoptosis, and proliferation and migration of macrophages caused by ox-LDL.[66] Xu et al provided evidence that tan-IIA reduces lesion size and atherosclerotic plaques stabilization in ApoE/mice by suppressing ROS production induced via oxidized LDL, the expression of TNF-α, IL-6 and MCP-1, and matrix metallo proteinase-9 (MMP-9) activity.[67] Zhao et al revealed that tan-IIA may have a role in the vulnerable plaques stabilization, mainly due to its NF-κB suppression, anti-inflammatory effects, phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and the RAGE axis which tends to reduced matrix degradation (MMPs-induced) and expression of an inflammatory factor in ApoE $^{-/-}$ mice.[68] Chen et al studies indicate that tan-IIA attenuate atherosclerosis by inhibiting miR-375 tend to activate KLF4, enhance autophagy and M2 polarization of macrophages.[69] Li et al study suggested that tan-IIA exerts an effect on atherosclerotic lesions by inhibiting DC maturation and reduced the expression level of pro-inflammatory cytokines. While hindering their potential to activate cytokine secretion and T-cell proliferation.[37]

TLRs are well-characterized pattern recognition receptors that induce the innate immune response and also impact the adaptive immune responses at different levels.[69] TLRs an important link between atherosclerosis and inflammation,[70] making it an attractive target for the treatment of cardiovascular diseases. Zhao et al results suggested that tan-IIA could stabilize vulnerable atherosclerotic plaque in ApoE$^{-/-}$ mice by reducing inflammation and immune response in a dose-dependent manner, and this anti-inflammatory and immune-regulating effect may be obtained by TLR4/MyD88/NF-κB signaling cascade.[71] These results also suggest that tan-IIA can induce an anti-inflammatory effect on RAW264.7 cells (LPS-induced) via reducing TLR4-MyD88-NF-κB signaling cascade, and regulating miRNA expression and a series of cytokine production.[72] Inflammatory stimuli induce the expression of VCAM-1 on the endothelial cells surface. In the initial phases of AS, VCAM-1 enhance the adhesion and migration of macrophages and leukocytes, and induced macrophages to take up lipids which gave them a foamy appearance.[73] VCAM-1 also promotes the adhesion of lymphocytes to endothelial cells.

In the later stages of AS, VCAM-1 is a key mediator of leukocyte recruitment to sites of inflammation and stimulates macrophages aggregation which ultimately induces MMP secretion, thereby degrading the fibrous cap.[74] Zhu et al found that STS reduced the production of

malondialdehyde (MDA), elevated the activity of superoxide dismutase (SOD), reduced the level of TNF-α and IL-6, and downregulated the expression of intracellular chloride channel 1 (CLIC1), ICAM-1, and VCAM-1 through its inhibition of CLIC1 expression as well as membrane translocation in the atherosclerotic mice.[75] The current study highlighted the clinical applications of tan-IIA on a pharmacological basis for the treatment of advanced atherosclerosis.

Regulate Endothelial Dysfunction (ED)

Tan-IIA and its derivatives remarkably inhibited oxidized LDL (oxLDL) uptake and the content of macrophage foam cell formation (induced by oxLDL). Tan-IIA also has an inhibitory effect against TSA of LOX-1 expression in macrophages, exploring the significant effect against atherosclerosis.[76] ED is thought to predict the occurrence of atherosclerosis and is therefore considered an early marker of the disease[77] and tan-IIA can control atherosclerosis by regulating endothelial dysfunction.

Studies have found that tan-IIA can improve endothelial function through the following mechanisms: Chen et al study[78] suggested that this compound covers endothelial function by suppressing strain-induced endothelin-1 (ET-1) expression, increasing ETB receptors and the formation of nitric oxide (NO), lowering ETA receptors, and upregulating endothelial nitric oxide synthase (eNOS) in Chronic intermittent hypoxia (CIH). According to Qian et al, this compound has a protective role in endothelial cells against oxidative stress factors such as H_2O_2 and methylglyoxal.[79] Zhu et al results indicated that tan-IIA may exert neuroprotective effects via increased pErk/Erk ratio and the expression of receptors for activated C kinase-1 (RACK1), and reduce the increased level of Beclin1 and LC3-II/I tends to inhibition of autophagy in the hippocampus (in mouse models of atherosclerosis).[80] Tang et al results suggested that the underlined compound suppresses the atherosclerotic lesions in $ApoE^{-/-}$ mice which may be due to decreased serum levels of oxLDL. The compound also decreases the mRNA expression of SR-A, CD36, and peroxisome proliferator-activated receptor-gamma (PPARγ) in aortas.[81]

Anti-Oxidants

Oxidative stress has a key role in atherogenesis which increases the demand for investigating significant antioxidants for the effective treatment of atherosclerosis. Recent studies have shown that tan-IIA reduce atherosclerosis by attenuating oxidative stress. Chen et al experiment suggested that tan-IIA prevents oxidative stress via lowering the production of oxLDL and elevates the activities of glutathione peroxidase (GPx) and SOD which might have a significant role in the atherosclerosis treatment. Tang et al results suggested that in rat model tan-IIA has the potency to attenuate atherosclerotic calcification (AC) which might be due to its inhibitory activity against oxLDL production (independent of the serum levels of lipids), calcium and 25-OH vitamin D (VD). Elevation in Cu/Zn SOD activity as well as mRNA and protein expression via tan-IIA might protect LDL against oxidation caused by superoxide anion in vessel.[80] Li et al results found that tan-IIA protected cultured macrophages from H_2O_2-induced cell death, increased GPx-1 mRNA levels, also significantly increased glutathione peroxidase (GPx) activities and protection was mediated in large part by tan-IIA induction of GPx gene expression and activity in animal models of atherosclerosis.[82]

Diabetes Mellitus

Diabetes mellitus (DM) is a chronic metabolic disease characterized[83] via hyperglycemia caused by impairment in insulin secretion or function, accompanied by abnormal metabolism of carbohydrates, proteins, and fats, which often leads to abnormal acid-base balance.[84] DM is a heterogeneous and complex disease that can be classified into type 1 and type 2 DM.[85] Although confounding factors such as dyslipidemia and hypertension are primarily associated with this chronic process. There is now sufficient evidence that diabetes alone can cause a large number of molecular changes in the heart.[77] Based on several reported studies, tan-IIA has a key contribution to the pathogenesis of diabetes.

Anti-Inflammation

Tan-IIA has been used in TCM for the treatment of a verity of inflammatory and cardiovascular disorders. Based on the correlation between inflammation and Type 2 diabetes, tan-IIA can serve as a candidate target for the treatment of diabetes via regulating inflammatory processes. Yuan et al studies have shown that in experimental rats, the underlined compound prevents inflammatory processes and overcome symptoms of Type 2 diabetes through 5′ AMPK signaling cascade stimulated via NF-κB.[86] Feng et al proved that the neuropathic pain in

diabetic rats' model has been lowered by tan-IIA through stimulating the Nrf2/ARE signaling cascade and attenuating the NF-kB signaling cascade.[78] Sun et al study showed that tan-IIA has remarkable cardioprotective effects given the diabetic cardiomyopathy. Tan-IIA also enhanced Akt and glycogen synthase kinase-3β phosphorylation and block the phosphorylation of NF-κB to lower the level of TNF-α, MPO and IL-6 activities by kinin B2 receptor-Akt-GSK-3β dependent pathway.[79] Li et al results revealed that STS can active the canonical Wnt pathway in partly, inhibit the expressed fractalkine induced by high glucose, and play a role of anti-inflammatory by regulating canonical Wnt pathway, thereby, it will provide an effective therapeutic target for DM and its complications.[87] Zhu et al studies also proved that pretreatment of ghrelin combined with STS reduces the apoptosis rate of HUVECs induced by high glucose environment and inhibits the expression of fractalkine via β-catenin/Wnt signaling pathway for DM and its complication.[88]

Regulate Endothelial Dysfunction (ED)

It has been suggested that the dysfunction of endothelium-dependent vasorelaxation has a key role in the development of cardiovascular complications in diabetes.[89] According to Li et al studies, Tan-IIA has significantly blocked the protein phosphatase 2A-A (PP2A) translocation from cytoplasm to the membrane and consequently decreased PP2A-A/eNOS interaction which leads to the prevention of eNOS dephosphorylation to cure diabetes via eNOS/NO cascade.[90] Across the globe, diabetic retinopathy is considered to be the most predominant and severe form of DM. Based on the results of Fan et al, VEGF and ICAM-1 expressions are remarkably downregulated via tan-IIA (in a dose-dependent manner) in hyperglycemia which reveals that under HG conditions, tan-IIA has an inhibitory effect on the vascularization, proliferation, and migration of human retinal endothelial cells (HREC).[91]

Anti-Oxidants

Tan-IIA has a potential role against oxidative stress and inflammatory processes. Oxidative stress contributes to the initiation as well as the progression of diabetic kidney disease. According to Chen et al, tan-IIA reduced the level of MDA and elevated the level of SOD because of its significant antioxidant property.[92] Chen et al experiment conformed that tan-IIA lowers the MDA content, 78-kDa glucose-regulated protein (Grp78), and expression of C/EBP-homologous protein (CHOP) via inducing SOD activity, decreased neuronal apoptosis, enhanced learning and memory through suppressing ER stress activation.[93]

Alzheimer's Disease

Alzheimer's disease (AD) is considered to be the worst form of dementia and the most prevalent among neurological disorders. AD is characterized by neuropeptides' abnormal regulation and aggregation of beta-amyloid (Aβ) precursors in the brain. Nerve inflammation, oxidative stress, and blocked neurotransmission are alterations that occur in the initial phase of sporadic AD, which manifests as mild cognitive impairment.[94,95] With the increase in aging, it has become a major problem in today's society. But, there is a lack of key approaches for the cure of AD. The clinical symptoms of this neurological disorder are manifested by increased forgetfulness or cognitive dysfunction, loss of language, and behavior. The neuropathological features of this disease include Aβ plaques, polymeric hyperphosphorylation of neurofibrillary tangles, amyloid angiopathy, nerve loss, and synaptic dysfunction.[96,97] In recent years, the famous TCM ie, *Salvia miltiorrhiza* which is commonly used in the cure of cardiovascular and cerebrovascular complications, exerts various neuroprotective effects and is increasing the attention for their use against AD.[82]

Anti-Inflammation

Recent studies indicated that inflammation is a part of a complex adaptive mechanism ("remodeling") that persists throughout the life cycle, and has the function of preventing or mitigating the endogenous process of tissue destruction and degenerative changes.[94] Lack of sufficient response against the inflammatory process can lead to severe inflammation and can spread locally (that is, from cell to cell) and systemic levels eg, via exosomes. AD is mainly linked with the neuroinflammatory process in the brain which leads to neuronal death. Nuclear factor of activated B-cells (NF-B) has a critical role in physiological inflammatory processes and can be a candidate target for AD therapy based on inflammation.[98,99] Besides, several reported studies have shown that tan-IIA has a significant contribution to the regulation of neuroinflammatory diseases. Tan-IIA treatment protects neurons through its anti-inflammatory activities. Li et al study

showed that in an AD model, tan-IIA administration can attenuate the development of astrocytes, lower the NF-κB level, and elevated the level of NeuN, Nissl body and IκB, as a result, tan-IIA exerts its neuroprotective and anti-inflammatory effects.[76] Lu et al study proved tan-IIA may represent a potential treatment in neurodegenerative diseases, such as AD to support the survival of neurons by reducing expression levels of glial fibrillary acidic protein, C3d, CD11b, C3c, C1q, IL-6 and IL-1β in brain tissues.[85] Zhang et al studies have shown that tan-IIA could lower the elevated expression of TNF-α, IL-1β and IL-6, attenuate the expression of monocyte chemoattractant protein 1 (MCP-1) and COX-2, decreased the protein expression of iNOS, and caused protein expression of nNOS in the spastic cerebral palsy (SCP) rats, which results in the regulation of the NF-κB and p38MAPK signaling cascades.[100] Jiang et al study revealed that the underlined compound significantly blocks the up-regulation of iNOS, matrix metalloproteinase-2 (MMP-2) as well as NF-κB/p65 in the RNA and protein expression levels of AD rats through the NF-κB pathway to reduces AD risk.[86] In summary, the underlined data indicate a more theoretical basis for the effective treatment of tan-IIA on behalf of neurodegenerative diseases and introduce a new perspective for the AD clinical treatment.

Anti-Oxidants

Oxidative stress-induced via amyloid β-peptide (Aβ) may have a key contribution to Alzheimer's disease (AD) pathogenesis.[101,102] It has been indicated that tan-IIA prevents oxidative stress and apoptosis. The basis of the mechanism is the ability to perform physiological adaptations by regulating various molecular and biochemical signal transductions that occur from the intracellular level of the entire brain to the network system level.[103] Liu et al proved that tan-IIA has a role in the protection of cultured cortical neurons against $A\beta_{25-35}$-induced neurotoxicity through its antioxidative effects via lowering the $A\beta_{25-35}$-induced increase of caspase-3 activity and decreased cytochrome C translocation from mitochondria into the cytosol, also enhanced the $A\beta_{25-35}$-induced Bcl-2/Bax ratio reduction in cortical neurons.[104] Tan-IIA potentially decreased elevated level of acetylcholinesterase (AChE) activity and malondialdehyde (MDA) level caused via STZ, and considerably blocked STZ induced reduction in SOD and glutathione peroxidase (GSH-Px) activities in the parietal cortex and hippocampus to ameliorating neuronal damage, restoring cholinergic function, attenuating oxidative stress and blocking p38 MAPK signal pathway activation.[105] These results strongly suggest that tan-IIA may be effective in treating AD associated with oxidative stress.

Induce Apoptosis of Tumor Cells

The aggregation of β-amyloid (Aβ) and neuronal death in the brain are pathological indications of AD.[106] Cell death is an important process for neuronal death in AD. Lin et al study revealed that Tan-IIA considerably enhanced the spatial learning and balance memory deficits caused via Ab1-42 in rats by shielding neuronal loss and decreasing the enhanced phosphorylation of tau protein via inhibiting ERK and GSK-3β signaling cascades.[104] Qian et al study proved that tan-IIA has a neuroprotective potential against the Aβ-induced cytotoxicity (through activation of Bcl-xL pNeuroprotection). The underlined compound also mediates neuropeptides that are correlated with the neuronal functions.[107] Zhong et al found that tan-IIA treatment may inhibit apoptosis by down-regulation of p53 and pp53 in rats, and in turn to protect neurons.[108]

Cancer

Across the globe, cancer is the second most prominent cause of death.[109] Many studies have confirmed the potential anticancer activities of tan-IIA. In the past decade, tan-IIA anticancer activity has aroused great interest. Tan-IIA is a natural anti-cancer agent extracted from *Salvia miltiorrhiza* and has anti-tumor activity. The anticancer effects and potential mechanisms of tan-IIA have been extensively studied in various cancer cell lines. Tan-IIA induces apoptosis through different molecular mechanisms and inhibits the spread of cancer.

Induce Apoptosis of Tumor Cells

Apoptosis is the death of a single cell or a small group of cells in the body. The cell plasma membrane will not be ruptured and will not cause the autolysis of dead cells. The normal human body eliminates damaged and mutated cells in the body through the mechanism of cell death, and cell apoptosis is usually inhibited during tumor development. When tumors occur, they can successfully induce apoptosis of tumor cells and will have a positive effect not only for the treatment of the primary tumor but also for the treatment of tumor recurrence and metastasis. Tan-IIA exerts its anti-tumor effects by promoting cell apoptosis. According to Chen et al,[110] tan-IIA suppresses the cell growth and accelerates the cellular apoptosis via downregulating of survivin in keloid fibroblasts. Given this, it is revealed that tan-IIA can effectively

participate in keloid treatment. These results indicated[111] that in nude mice, the underlined compound considerably reduced HepG2 cell-based tumor growth (in a dose-dependent manner), and stimulate cell death rate through elevated up-regulation of CYP2J2 expression. Based on the reported study,[111] tan-IIA may stimulate the apoptotic process of hepatocellular carcinoma via miR30b-p53-PTPN11 /SHP2 cascade, effect apoptotic molecules ie, Bax/Bcl2, cleaved caspase 3 and the regulating factors of the cell cycle, such as p21, CDK6, cyclin D1. According to the reported study,[112] tan-IIA enhances the apoptotic process through blockage of Wnt/β-catenin-dependent MGMT expression. These results provide extensive knowledge and understanding to explore the mechanistic pathway through which *Salvia miltiorrhiza* act against tumor progression. The underlined results[113] revealed that TSA chemosensitizer colon cancer cells and enhance cellular apoptosis, attenuation of NF-κB activation with inhibitor ie, pyrrolidine dithiocarbamate, elevated the enhanced apoptosis via lowering NF-κB signaling cascade. Tan-IIA[114] caused cell death via a mitochondria-dependent pathway in the bladder carcinoma cells. The combined therapy of tan-IIA with a low dose of cisplatin effectively caused the death of bladder carcinoma cells. The underlined results revealed that tan-IIA can act as a leading anti-cancer agent in bladder carcinoma.

Inhibition of Tumor Cell Migration and Proliferation

Based on the existing studies on tan-IIA, it can inhibit tumor cell migration and proliferation. The results[113] revealed that TSN block SGC-7901 cell proliferation and migration via downregulating FOXM1 and has a significant effect against cancer progression. Moreover, high-dose of tan-IIA[115] attenuate astrocytoma cell growth and development, and migration. Tan-IIA also enhances the apoptotic process via the Notch-1 pathway. Because of these results, tan-IIA may use as a leading compound for the development of effective drugs against astrocytoma.

Side Effects and Toxicity

Even though Salvia miltiorrhiza has been used for many decades, the toxic effects of the tan-IIA (derived from *Salvia miltiorrhiza*) are still understudied. Traditional Chinese medicine injection is a unique drug variety in China and is widely used in clinical practice. However, due to its complex composition, its adverse reaction events are more frequent, and the safety of traditional Chinese medicine injection has attracted a lot of attention. With the increasing clinical applications, the adverse reactions of Danshen injection include allergic reaction, bradycardia, tachycardia, drug-induced hepatitis, diarrhea, muscle tremor, and uremia.

Cao et al evaluate the hormesis effect, hemolytic effect, and anaphylaxis of sodium tan-IIA sulfonate injection in cavy and rabbit. According to Wang et al survey, chorionic and dechorionated zebrafish embryos were used for the evaluation of developmental and acute toxicity of tan-IIA. Then they observed the lethality as well as teratogenicity at various concentrations of tan-IIA.[116] The underlined study may prevent the risk of its use in clinical practice. The aqueous extract of Danshen (via injections) is mostly used in China as a traditional Chinese remedy against cardiovascular complications. These results revealed that chronic or sub-chronic administration of Danshen injection was found to be lower or non-poisonous in both male and female rats, and the no-observed-adverse-effect level (NOAEL) for sub-chronic administration of Danshen injection dose was 5.76g/kg bw/day, however, Danshen injection were found to be associated with focal inflammation in a dose-dependent manner.[117]

Conclusions and Future Perspectives

As a traditional Chinese medication for enhancing blood circulation and clearing blood stasis, *Salvia miltiorrhiza* has been commonly used against clinical cardiovascular and cerebrovascular diseases, with remarkable curative effect and minute adverse reactions. In summary, tan-IIA not only has antioxidant effects, anti-atherosclerosis, and other cardiovascular pharmacological effects and antibacterial and anti-inflammatory effects, but more importantly, it has anti-tumor effects. Its anti-tumor mechanism may be involved in the enhancing of tumor cell differentiation and apoptosis. At present, tan-IIA has been widely used in the clinical non-tumor field. Tan-IIA is a promising new candidate target to be used as an anti-tumor drug in clinical practice and contribute to the treatment of malignant tumors. In-depth research on tan-IIA is being carried out worldwide, which may expand the effective clinical uses of the underlined compound and its different dosage forms. At the same time, new formulations and synthetic analogs with elevated bioavailability and reduced side effects are also under development. In-depth research on tan-IIA and

Salvia miltiorrhiza is of great significance to the effective use of Chinese herbal medicine and to promote the status and influence of Chinese medicine on the international stage.

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Disclosure

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