Leonurus japonicus: A promising anticancer Chinese medicine modulating regulated cell death

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To the Editor: According to the latest statistics published by National Cancer Center of China, approximately 4,824,700 cancer cases were newly diagnosed and 2,574,200 patients died from cancer in China in 2022.[1] Uncontrolled cell proliferation and physiological death resistance, which are the most representative cancer characteristics, complicate the process of restoring health and restrict treatment effectiveness in clinical practice.[2] Regulating multiple cell-death pathways to reprogram cancerous suicide has emerged as a promising approach to achieve valuable drugs discovery. Given the use of *Leonurus japonicus* as a historical folk medicine, relative hypotoxicity, and malignancy-inhibiting properties, it has shifted scientists' attention to mining its diverse active components and determining its pharmacological activities, thereby paving the way for its administration in clinical cancer treatment.

Leonurus japonicus, the most common *Leonurus* species in China, has cardioprotective, antioxidant, and many other pharmacological activities. To date, approximately 280 chemical compounds have been isolated and extracted from *Leonurus japonicus*. Based on distinct structural characteristics, the active components can be classified into diverse categories, such as alkaloids, terpenes, flavonoids, and steroids.[3] Alkaloids are the most representative classes in all categories of *Leonurus japonicus* extracts. The alkaloids leonurine and stachydrine are frequently used as reference substances for quality control of *Leonurus japonicus* usage in the Pharmacopoeia of the People's Republic of China. In addition, a series of flavonoids (e.g., rutin, quercetin, and luteolin) have gradually become research hotspots for pharmacological exploration.

Distinguished from accidental cell death, regulated cell death (RCD) is modulated by a series of specific signal transduction pathways, including the widely investigated apoptotic pathway, as well as other cell death modalities.[2] This article summarized three crucial cell death pathways involved in cancerous-treating mechanisms of *Leonurus japonicus* and its active compounds, which are named as apoptosis, pyroptosis, and ferroptosis.

Apoptosis is a combined effect of pro- and anti-apoptotic factors, and the proportion of the above two distinct effects determines whether cancer cells undergo systematic survival or death.[4] Phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway is regarded as the most crucial functional pathway in regulating cell apoptosis, which can activate mitochondrial-mediated intrinsic pathway to assist cancerous cell survival.[5] In U937 and THP-1 acute myeloid leukemia cells, alcoholic extracts of *Leonurus japonicus* (ethanol concentration: 99.0%, extraction yield: 16.7%) repressed PI3K/AKT signaling pathway by increasing intracellular reactive oxygen species (ROS) production, and also triggered endoplasmic reticulum (ER)-associated apoptosis to present obvious cytotoxicity.[6]

Mitogen-activated protein kinase (MAPK) signaling pathway is a momentous component of the eukaryotic cell signaling transduction network, indispensably affecting physiological and pathological processes, including cell proliferation, differentiation, and apoptosis.[7] Quercetin inhibited P38/MAPK phosphorylation, and markedly upregulated cell cycle inhibitors such as P16 and P21, thereby inducing selective apoptosis against breast cancer MCF-7 cells.[8] By upregulating the mRNA levels of several dual-specific phosphatases (DUSPs), luteolin inhibited extracellular-regulated kinase 1/2 (ERK1/2) phosphorylation and eventually activating apoptosis via the intrinsic pathway in the human gastric cancer BGC-823 cells.[9]

The initial discovery of caspase-1-dependent cell death in *Salmonella*-infected macrophages, uncovered a new

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cell death subroutine initially referred to as pyroptosis. Pyroptosis specifically reprograms systemic or localized immune responses to alter tumor microenvironment and restrain tumor development.[10] Luteolin robustly inhibited tumor growth by activating caspase-1/nod-like receptor thermal protein domain associated protein 3 (NLRP3)/gasdermin D (GSDMD)-mediated pyroptotic process. Mechanistically, it stimulated ROS and superoxide dismutase (SOD) generation to elicit interleukin-1 beta (IL-1β)-mediated oxidative stress in HT29 cells and xenograft nude mice.[11] Quercetin significantly triggered growth arrest in colon cancer by upregulating protein levels of NIMA-related kinase 7 (NEK7), consequentially activating NLRP3 inflammasome-GSDMD pathway.[12]

Owing to its participation in mediating metabolic imbalance to eliminate cancer cells, ferroptosis is regarded as an alternative therapy to remedy inherent escape involved in cancer development.[13] Leonurine inhibited cancer proliferation and markedly activated ferroptosis in PC3 and DU145 prostate cancer cells by targeting miR-18a-5p/solute carrier family 40 member 1 (SLC40A1) pathway.[14] Oleanolic acid demonstrated potent ferroptosis-inducing properties both *in vivo* and in Hela cells. The upregulation of acyl-coenzyme A (CoA) synthetase long chain family member 4 (ACSL4) and transferrin receptor 1 (TfR1) stimulated Fe^{3+} metabolism, leading to enlargement of the labile iron pool, eventually resulting in cell death [Figure 1].[15]

Currently, various treatments like chemotherapy and radiotherapy are continuously being improved in clinical cancer treatment.[16] Many formulations including *Leonurus japonicus* tablets, capsules and injections, have gradually been developed. However, there still exist lots of challenges in the smooth transition between fundamental research and clinical application. On the one hand, pharmacokinetic weaknesses of isolated components, particularly those with limited solubility and low stability, add the complexity to apply appropriate compounds in practical cancer treatment. Thus, devising meaningful approaches to achieve higher bioavailability is critical for practical cancerous application. On the other hand, the anticancer investigations of *Leonurus japonicus* are still in

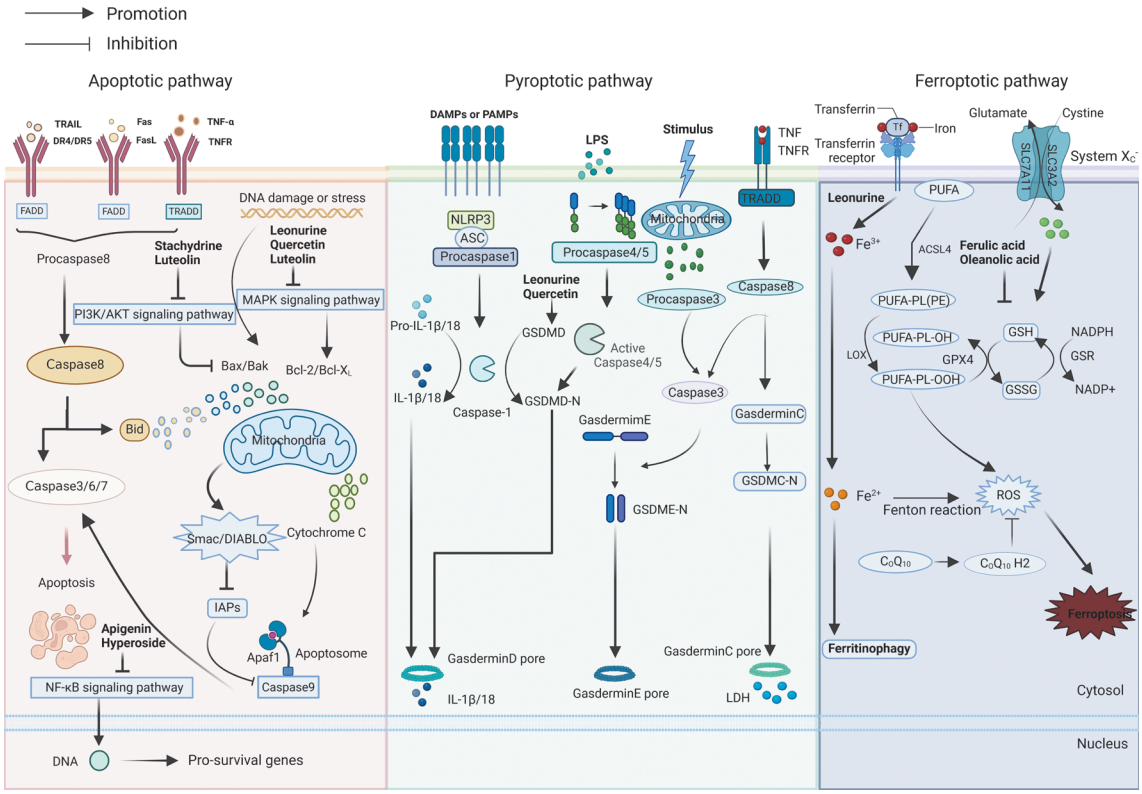

Figure 1: Major types of RCD in cancer treated with *Leonurus japonicus* or its active component. ACSL4: Acyl-CoA synthetase long-chain family 4; Apaf1: Apoptotic protease activating factor-1; ASC: Apoptosis-associated speck-like protein containing a caspase recruitment domain; Bad: Bcl-2 antagonist/killer; Bak: Bcl-2 antagonist/killer 1; Bax: Bcl-2-associated X; Bcl-2: B-cell lymphoma-2; Bcl-X_L: B-cell lymphoma-extra large; Bid: Bcl-2 homology 3 interacting domain death agonist; CoQ_{10}: Coenzyme Q_{10}; CoQ_{10} H2: Reductive Coenzyme Q_{10}; DAMPs: Damage associated molecular patterns; DR4/5: Death receptors 4/5; FADD: Fas-associating protein with a novel death domain; Fas: Factor-related apoptosis; FasL: Factor-related apoptosis ligand; FSP1: Ferroptosis-suppressor-protein 1; GPX4: Glutathione peroxidase 4; GSDMD: Gasdermin D; GSDMC-N: Gasdermin C-N domain; GSDMD-N: Gasdermin D-N domain; GSDME-N: Gasdermin E-N domain; GSH: Glutathione; GSR: Glutathione-Disulfide Reductase; GSSG: Oxidized glutathione; IAPs: Inhibitor of apoptotic proteins; IL-1β/18: Interleukin-1beta/18; LDH: Lactate dehydrogenase; LOX: Lysyloxidase; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinase; $NADP^+$: Oxidized nicotinamide adenine dinucleoside phosphate; NADPH: Nicotinamide adenine dinucleotide phosphate; N-GSDMD: Gasdermin D-N domain; NF-κB: Nuclear factor kappa-B; NLRP3: Nod-like receptor thermal protein domain associated protein 3; PAMPs: Pathogen-associated molecular patterns; Pro-IL-1β/18: Interleukin-1β/18 precursor; PUFA: Polyunsaturated fatty acid; PUFA-PL-OOH: PUFA phospholipid hydroperoxide; PUFA-PL-OH: PUFA phospholipid alcohol; PUFA-PL(PE): PUFA-containing phospholipids; RCD: Regulated cell death; ROS: Reactive oxygen species; SLC3A2: Solute Carrier Family 3 Member 2; SLC7A11: Solute Carrier Family 7 Member 11; Smac/DIABLO: Second mitochondria-derived activator of caspases/Direct inhibitor of apoptosis-binding protein with low pI; Tf: Transferrin; TNF-α: Tumor necrosis factor-α; TNFR: Tumor necrosis factor receotor; TRADD: Tumor necrosis factor receptor-associated death domain protein; TRAIL: Tumor-necrosis factor related apoptosis-inducing ligand.

the preliminary stage and need to be further developed and deepened, with a greater emphasis on animal experiments and clinical trials, to ensure the safety and effectiveness of *Leonurus japonicus* in anticancer treatment.

In summary, many active compounds originating from *Leonurus japonicus*, especially flavonoids and alkaloids, exhibit curative properties in multiple cancers, and therefore can be deemed as prospective anticancer agents in the field of clinical application. Hopefully, the enormous capacity of *Leonurus japonicus* to manage malignancies by affecting RCD will eventually enable its use in cancer treatment in the real-world setting. The clear potential for enhancing the pharmacokinetic characteristics of *Leonurus japonicus* and the future elucidation of its pharmacological basis will aid in this endeavor.

Conflicts of interest

None.

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