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Review Article

Tumor suppressive role of rottlerin in cancer therapy

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Abstract: Cancer as a major public health problem is a big trouble to be cured at present in the world. Thus, it is essential to discover better anticancer drugs to treat cancer patients. It has been reported that rottlerin, a natural polyphenolic compound from the mature fruits of Mallotus philippinensis, possesses multiple anti-cancer biological activities. Rottlerin exhibited its antitumor property in a variety of human cancers, suggesting that rottlerin could be a potential agent for treating cancers. In this review we discuss the recent literature regarding the biological functions and tumor suppressive mechanisms of rottlerin in cancers. We hope rottlerin will be further exploited for potential treatment of human cancers.

Keywords: Rottlerin, cancer, therapy, target, antitumor

Introduction

Since cancer is a major health trouble in the world, some researchers have been working on exploring the mechanisms of cancer development and progression. The discovery of these mechanisms could contribute to better understanding of cancer pathophysiology, which could lead to the development of new targets and drugs [1]. It has been known that drug discovery from medicinal plants has played an important role in the treatment of cancers. Indeed, a lot of available anticancer drugs are natural products or natural product-derived drugs, or natural product mimics [2]. Thus, it is pivotal to develop new natural agents as potential anti-tumor drugs.

The mallotus philippinensis muell, also known as Kamala, is very common perennial shrub or small tree and widespread distribution, from the western Himalayas, through India, Sri LanKa, to southern China, and throughout Malesia to Australia [3]. Kamala tree withstands considerable shade, frost-hardy and resistant to drought. Rottlerin is a natural polyphenolic compound from the mature fruits of mallotus philippinensis [3]. The IUPAC name of rottlerin is (E)-1-[6-[(3-acetyl-2,4,6-trihydroxy-5-methylphenyl)methyl]-5,7-dihydroxy-2,2-dimethylchromen-8-yl]-3-phenylprop-2-en-1-one. The molecular formula of the structure is $C_{30}H_{28}O_8$, which has a molecular weight of about 516 g/mol [4] (**Figure 1**). Multiple studies have demonstrated that rorrlerin inhibits some protein kinases, such as PKCδ (protein kinase C δ), CaM-kinase III (calcium/calmodulin-dependent protein kinase), PRAK (p38-regulated/activated protein kinase), MAPKAP-2 (mitogen-activated protein kinase-activated protein kinase 2), Akt/PKB (protein kinase B) [5, 6], suggesting that rottlerin is a very versatile substance. Therefore, this drug processed various biological activities, such as anti-filarial, anti-bacterial, anti-inflammatory, and regulatory activity [7]. Rottlerin is used as purgative, anthelmintic, vulnerary, detergent, maturant, carminative, and alexiteric [3]. Rottlerin has mitochondrial uncoupling properties that cause ATP depletion and inhibition of cellular processes controlled by phosphorylated molecules [8]. As mentioned above, rottlerin is an inhibitor of some protein kinases that are involved in cancer processes, indicating that rottlerin could interrupt the pro-

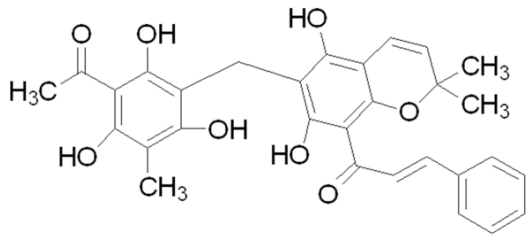

Figure 1. The structure of rottlerin.

cess of cancer progression. Indeed, some reports have revealed that rottlerin exhibits antitumor activities in a variety of human cancers.

Role of rottlerin in human cancers

Rottlerin was found to possess some anti-cancer biological activities [9-11]. Rottlerin exhibited its antitumor property including inhibition of cell growth, induction of apoptosis, triggering cell cycle arrest, retarding cell migration and invasion in various types of human cancer. These reports dissect that rottlerin could be a potential agent for treating cancers. In the following paragraphs, we will describe the recent literature regarding the biological functions and tumor suppressive mechanisms of rottlerin in multiple human cancers.

Rottlerin in lung cancer

In the United States, although lung cancer incidence rates continue to decline in 2018, it is still the major cause of morbidity and mortality [12]. Non-small cell lung cancer (NSCLC) comprises approximately 85% of all lung cancers, which has become a leading cause of cancer-related mortality [13]. Despite the progress in radical resection and adjuvant therapy (radiotherapy and chemotherapy) after surgery, NSCLC patients still have a poor 5-year survival rate [14]. Several signaling pathways have been involved in lung tumorigenesis. For example, MAP kinase (MAPK) cascades play a central role in the cellular response to various extracellular stimuli [15, 16]. Three subgroups of MAPKs are known: extracellular signal regulated kinases (ERK1/2), Jun N-terminal kinase/stress activated protein kinase (JNK/SAPK), and p38. Activation of MAPK members has been implicated in the regulation of apoptotic cell death [17]. Rottlerin was reported to reverse the protein expression of many kinases of prosurvival signaling pathway, such as Ras, ERK, and p38, during the photoactivated lonicera japonica extract-induced cell death [18]. The Hippo signaling pathway plays a central role in the regulation of tissue and organ size during development via deregulation of stem cell proliferation and apoptosis [19]. TAZ (transcriptional co-activator with a PDZ-binding domain) activity is associated with tumor differentiation and prognosis [20]. Our study reveals that rottlerin exerted its tumor suppressive function via inactivation of TAZ in NSCLC cells [21]. Therefore, rottlerin could be a potential agent for the treatment of lung cancer.

Rottlerin in breast cancer

Breast cancer is the most prevalent cancer diagnosed in women and the second most common cancer in global with heterogeneous pathological features [12, 22]. The result of cancer statistics shows that approximately 266,120 new cases of female breast cancer will be occurred in the United States in 2018. The estimated deaths numbers of breast cancer will be 40,920 cases in 2018 [12]. In a large majority of breast cancer cases, cyclin-D1 is overexpressed and its level is correlated to negative prognosis [23, 24]. Transcription factors such as Ap-1, Sp-1 and NF-κB (nuclear factor kappa B) are known to regulate the cyclin-D1 gene transcription [25]. It has been reported that rottlerin blocked MCF-7 cell proliferation through PKC-, ERK-, p21/27-, and Akt-independent manner involving the sequential inhibition of NF-κB/cyclin-D1 [26]. One study has observed that rottlerin is capable of triggering caspase-dependent or autophagic, caspase-independent cell death, depending on the functional availability of caspase-3 in MCF-7 cells [27]. Recently, Kumar et al. reported that rottlerin could induce extensive cytoplasmic vacuolization in breast cancer stem cells. This study showed that autophagy inhibitors suppress the formation of cytoplasmic vacuolization, indicating that there might be interaction between autophagy and apoptosis induced by rottlerin [28]. Being downstream of Akt, mTORC1 (mammalian target of rapamycin complex 1) is an essential effector in driving cell proliferation and susceptibility to oncogenic transformation [29-31]. One study indicates that rottlerin is a novel LRP6 (low-density lipoprotein receptor-related protein 6) inhibitor and suppresses both Wnt/β-catenin and mTORC1 signaling in

breast cancer cells, and that LRP6 represents a potential therapeutic target for cancers [32]. In addition, Skp2 (S-phase kinase associated protein 2) has been revealed to critically enhance the pathogenesis of breast cancer [33]. One study discovered that rottlerin suppressed cell migration and invasion in breast cancer cells, and identified that rottlerin exhibited its anti-tumor potential partly through inactivation of Skp2 in breast cancer [34].

Rottlerin in prostate cancer

Prostate cancer is the most common cancer and the second leading cause of cancer death in American males [12]. In the world, the death of 300,000 patients per year and its incidence kept on increasing during the last two decades [35]. Although there are some ways to suppress localized tumors, such as cryoablation, chemotherapy, radiotherapy, and radical prostatectomy, it is still no effective treatment for patients with recurrent or metastatic prostate cancer [36]. Moreover, the hormone-refractory prostate cancer (HRPC), which is resistant to hormone therapy, is a major obstacle in clinical treatment [37]. It is known that EGFR (epidermal growth factor receptor) is overexpressed in a variety of solid tumors including prostate, breast, brain, bladder, and lung cancers [38-40]. Furthermore, the studies demonstrated that the overexpression of EGFR is correlated with tumor invasion and metastasis [41]. Therefore, targeting EGFR could be useful for the treatment of these cancers. In fact, inhibition of PKCδ expression by rottlerin reduced migration and invasion of prostate cancer cells through the downstream of EGFR signaling [42].

In addition, the nuclear proteins topoisomerases are enzymes that are responsible for DNA topology. Inhibition of the topoisomerase I can cause severe DNA damage response and activate DNA damage-related molecules, leading to an ultimate cell death [43]. One study dissected that rottlerin-mediated camptothecin sensitization is through the augmented stabilization of TOP1cc (topoisomerase I-DNA cleavage complexes), leading to an increase of DNA damage stress and an impairment of DNA repair capability [43]. Subsequently, mitochondria-involved apoptosis is triggered through Bax activation and truncated Bad formation [44]. Autophagy plays an important role in the conservation of cellular energy and cell survival in stress condition [45]. Notably, the PI3K (phosphatidylinositol-3 kinase)/Akt/mTOR and AMPK signaling pathway are key regulators of autophagy and apoptosis. It has been reported that rottlerin induced autophagy and apoptosis in prostate cancer stem cells via PI3K/Akt/mTOR signaling pathway [46]. Strikingly, rottlerin induced Wnt co-receptor LRP6 degradation, and suppressed both Wnt/β-catenin and mTORC1 signaling pathways in prostate cells [32]. These reports revealed that rottlerin could be a promising agent for treating prostate cancer.

Rottlerin in pancreatic cancer

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States. The overall 5-year survival rate remains less than 8% and has not been improved significantly for several decades [12, 47]. It has been accepted that PKC plays a key role in the mechanism of action of the pancreatic secretagogues such as acetylcholine (Ach) and cholecystokinin (CCK) [48-50]. Although rottlerin is considered as an inhibitor of PKCδ, its effects in pancreatic acini are not due to inhibition of PKCδ, but likely due to its negative effect on acini energy resulting in ATP depletion [51]. Another study provided evidences to demonstrate that rottlerin has a potent proapoptotic and antitumor activity in pancreatic cancer, which is mediated by disrupting the interaction between prosurvival Bcl-2 proteins and proapoptotic BH3-only proteins [52]. The PI3K/Akt/mTOR pathway is implicated in the pathogenesis of pancreatic ductal adenocarcinoma (PDAC) [53, 54]. Recently, rottlerin has been shown to induce a starvation response, which is a key regulator of autophagy causing its induction in pancreatic cancer cells [55]. Consistently, rottlerin induced early autophagy as a survival strategy against late apoptosis through PKCδ-independent, but dependent on PI3K/Akt/mTOR cascade in pancreatic CSCs (cancer stem cells) [56]. Notch signaling pathway is evolutionary conserved and plays critical roles in neurogenesis, myogenesis, vasculogenesis, and hematopoiesis [57]. Sonic Hedgehog (Shh), a member of the hedgehog (Hh) family, plays a significant role in pancreatic cancer progression in both sporadically or in genetically pre-

disposed individuals [58, 59]. In a parallel study, rottlerin exhibited a significant inhibition of Akt, Shh, and Notch pathways [60]. Moreover, rottlerin induced apoptosis and inhibited pancreatic cancer cell growth by targeting Akt, Notch and Shh signaling pathways [60]. Remarkably, rottlerin was found to suppress Skp2 expression and subsequently exerts its tumor suppressive function in pancreatic cancer cells [61]. Thus, rottlerin represents a novel agent for pancreatic cancer treatment.

Rottlerin in colon carcinoma

Colorectal cancer (CRC) is the third most common cancer diagnosed and the fourth cause of cancer death in the world [62]. CRC patients often have a poor prognosis [63]. The CRC development is a multistep process that often is involved in the genetic alterations. The mutations of proto-oncogenes and tumour suppressor genes are common reasons to make the transformation of normal cells into malignant cells. This transformation leads to anomalous multiplication, self-sufficiency with respect to growth signals, insensitivity to growth inhibitor signals and evasion of apoptosis [64]. MACC1 (metastasis-associated in colon cancer 1) has been characrized as a promising biomarker for prognosis of metastasis formation, survival, and prediction of therapy response in multiple cancer types including CRC [65-68]. In line with this, MACC1 expression was shown to be directly correlated with metastasis formation and metastasis-free survival in CRC [69]. MACC1 may be a therapy target for patients with CRC. Rottlerin was found as the inhibitor of MACC1 to restrict colon cancer progression and metastasis [70]. Further study demonstrated that rottlerin affected mitochondrial function independent of PKCδ, thereby sensitizing cells to TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) in CRC [71]. NF-κB is generally overexpressed in CRC cancer, which is involved in cell cycle control, apoptosis, proliferation, and survival of malignant cells [72]. It has been demonstrated that rottlerin inhibited the activity of NF-κB pathway in human CRC [73]. Altogether, rottlerin could be an anticancer agent for CRC.

Rottlerin in hepatocellular carcinoma

Primary hepatic cancer, also known as hepatocellular carcinoma (HCC), is the sixth most common cancer and is considered as the common leading cause of cancer-related deaths worldwide [74]. HCC often develops within an established background of chronic liver disease (70-90% of all patients). The most frequent risk factor for HCC is chronic HBV infection, which accounts for more than 50% of all HCC cases [75]. HCC incidence is increased with viral load and duration of infection [76], suggesting an accumulated risk of long-lasting oncogenic damage. DEAD-box RNA helicase 3 (DDX3), which belongs to DEAD-box family proteins, is reported to play a critical role in cancer development and progression [77]. It has been known that DDX3 is a tumor suppressor in HCC, implying that upregulation of DDX3 could be helpful for HCC treatment. Wang et al. found that rottlerin upregulated DDX3 expression and subsequently downregulated Cyclin D1 expression and increased p21 level in HCC cells, suggesting that rottlerin exhibits its anti-cancer activity partly due to upregulation of DDX3 in HCC [78]. Shi et al. reported that rottlerin inhibited cell growth, migration and invasion in HCC cells partly through the inhibition of TAZ [79]. Taken together, rottlerin could be a new agent for HCC treatment.

Rottlerin in glioma

Among primary malignant brain tumors, 80% tumors are malignant gliomas (MGs). Glioblastoma multiforme (GBM) accounts for more than half of MG cases [80]. Malignant gliomas, which are common primary tumors of the central nervous system, present a particular therapeutic challenge. The reasons are due to that gliomas are invasive and not amenable to complete surgical removal. Moreover, glioma cells are refractory to traditional chemotherapy and radiotherapeutic approaches, leading to poor prognosis [81]. Dysregulation of signaling pathways is a characteristic feature in gliomas [82, 83]. Protein kinase C (PKC) and Raf-1 were two key molecules with upregulation in malignant gliomas [84-86]. The Raf-1 cascade is one of the main systems for the transduction of proliferative signals through the cytoplasm [87, 88]. PKC could activate ERK and MAPK pathways in cancer. Rottlerin has been reported to potentiate the antineoplastic effects through inhibition of ERK and Akt phosphorylation, and subsequent down-regulation of cyclins and cdks, resulting in inhibition of cell proliferation and

migration in human glioma cells [89]. Cdc20 (cell division cycle 20) was reported to be a pivotal factor in maintaining tumorigenic glioma tumor initiating cells through degradation of p21 and regulation of Cdc25C (cell division cycle 25C), c-Myc, and Survivin [90]. In a parallel study, rottlerin could exert its tumor suppressive function by inhibiting Cdc20 pathway, which is constitutively active in glioma cells [91]. In a word, rottlerin could be used for the treatment of gliomas.

Rottlerin in melanoma

Cutaneous melanoma is a malignancy arising from melanocytes in a multistep pathway. A worldwide increase in melanoma incidence has been observed in the past decades, especially a fivefold increase in Caucasians alone. Melanoma has become the sixth leading cause of death in the USA [92, 93]. The estimated new cases of melanoma is 91,270 in America in 2018 [12]. Standard therapy for primary melanoma, satellite, and in-transit metastases is surgery [94]. Rottlerin was found to regulate the expression of cyclin D1, p21/Cip1, ERK, Akt, and NF-κB in melanoma cells, leading to cell growth inhibition, and cell cycle arrest [95]. It has been known that eIF4F (eukaryotic translation initiation factor) inactivation is emerging as a promising approach for anti-cancer intervention [96-98]. The eIF4E is controlled by 4E-BP and one study discloses a novel mechanism of rottlerin-induced cancer cells death via mTORC1/4EBP-1 inhibition in melanoma cells [99]. It is required to further investigate whether rottlerin could be a pivotal agent for treating melanoma.

Rottlerin in gynecological cancers

Numerous studies have clarified that rottlerin exhibited tumor suppressive function in gynecological cancer. For example, rottlerin has been identified to induce down-regulation of caspase-2 in cervical cancer cells and ovarian cancer cells, which was independent of its ability to inhibit PKCδ [100]. Moreover, rottlerin-triggered caspase-2 down-regulation was proteasome-mediated pathway in gynecological cancer cells [100]. Another study reported that gonadotropins induced ovarian cancer cell proliferation and migration via activation of ERK1/2 signaling, which was inhibited by rottlerin, suggesting that gonadotropins promoted cell growth and migration via PKCδ-dependent manner [101]. Strikingly, rottlerin was identified to inhibit ovarian cancer cell proliferation in a dose-dependent manner [102]. Furthermore, the group I Pak inhibitor sensitized cells to the cytotoxic effects of rottlerin in ovarian cancer [102]. These reports clearly validate that rottlerin exhibits the anti-tumor potential in gynecological cancer.

Rottlerin in other human cancers

In bladder cancer cells, rottlerin treatment led to cell apoptosis via induction of autophagy to achieve the effect of antitumor [103]. Thyroid cancer with an increased incidence is the most common neoplasm of the endocrine system [104]. The prognosis of follicular thyroid carcinoma is associated with metastatic status [105]. The follicular thyroid carcinoma cells after rottlerin treatment exhibited altered morphology, reduced adhesion to extracellular matrix, decreased migration ability via inhibition of integrin β1, FAK, and reduced activity of Rho GTPases [106]. In nasopharyngeal carcinoma, rottlerin-induced anti-cancer activity via inhibition of Notch-1 signaling pathway [107]. PKC-δ is a putative downstream target of PI3K in B-CLL (chronic lymphocytic leukaemia) [108]. In CLL, rottelrin decreased the expression of the important anti-apoptotic proteins Mcl-1 and XIAP accompanied by a loss of the mitochondrial membrane potential [109]. Phospholipase D (PLD) is a ubiquitous enzyme that can be activated by ATP (adenosine 5'-triphosphate) or PMA (phorbol 12-myristate 13-acetate) in B-lymphocytes from CLL. Rottlerin inhibits P2X7 receptor-stimulated PLD activity in B-CLL [110]. We believe that rottlerin will be found to exert its anti-tumor activity in a majority of other human cancers.

Conclusions

Mallotus philippinensis has been widely used as traditional medicine in several parts of countries including India [111]. Rottlerin, isolated from M. philippinensis, has presented significant anticancer activities in a variety of human tumors via different mechanisms (**Table 1**). In this regard, rottlerin, as a promising therapeutic agent, might possess a prospect to bring about the better treatment outcomes due to

Table 1. Summary of the functions of Rottlerin in human cancers

Cancer Type	Rottlerin Function	Reference
Lung cancer	Down-regulation of TAZ, inhibited cell growth, triggered apoptosis, arrested cell cycle, and retarded cell invasion	[21]
Breast cancer	Inhibited cell growth, cell migration and invasion, induced apoptosis and cell cycle arrest. Inhibited the NF-κB/cyclin-D1, induced extensive cytoplasmic vacuolization; suppressed Wnt/β-catenin and mTORC1; inactivation of Skp2	[26-28, 32, 34]
Prostate cancer	Inhibited PKCδ, reduced migration and invasion; mediated camptothecin sensitization via the augmented stabilization of TOP1cc; induced autophagy and apoptosis via PI3K/Akt/mTOR; induced LRP6 degradation, and suppressed Wnt/β-catenin and mTORC1	[32, 42, 44, 46]
Pancreatic cancer	A potent proapoptotic and antitumor activity; disrupting the interaction between Bcl-2 and BH3-only proteins; induced early autophagy through dependent on PI3K/Akt/mTOR cascade; induced apoptosis and inhibited growth by targeting Skp2, Akt, Notch and Shh	[52, 56, 60, 61]
Colon carcinoma	The inhibitor of MACC1 to restrict progression and metastasis; affected mitochondrial function, sensitizing cells to TRAIL; inhibition of NF-κB	[70, 71, 73]
Hepatocellular carcinoma	Upregulated DDX3 expression and downregulated Cyclin D1 and increased p21 level; inhibition of TAZ, inhibited cell migration and invasion	[78, 79]
Glioma	Inhibition of ERK and Akt phosphorylation and down-regulation of cyclins and cdks, inhibited cell proliferation and migration; inhibiting Cdc20	[89, 91]
Melanoma	Inhibition of NF-κB nuclear migration and ERK activity and growth arrest; induced cancer cells death, and mTORC1/4EBP-1 inhibition	[95, 99]
Gynecological cancer	The cytotoxic effect of other agents in ovarian cancer cells was significantly enhanced by rottlerin; rottlerin was identified to inhibit ovarian cancer cell proliferation; induced down-regulation of caspase-2 in cervical cancer cells and ovarian cancer cells.	[100, 102]
Bladder cancer	Induced autophagy to achieve the effect of antitumor	[103]
Thyroid cancer	Altered morphology, reduced adhesion to extracellular matrix, decreased migration ability; decreased protein levels of integrin β1, FAK, focal adhesion complex constituents, and reduced activity of Rho GTPases	[106]
Nasopharyngeal carcinoma	Inhibition of Notch1; suppressed cell growth, migration and invasion	[107]
Lymphocytic leukaemia	Inhibited P2X7 receptor-stimulated phospholipase D activity	[110]

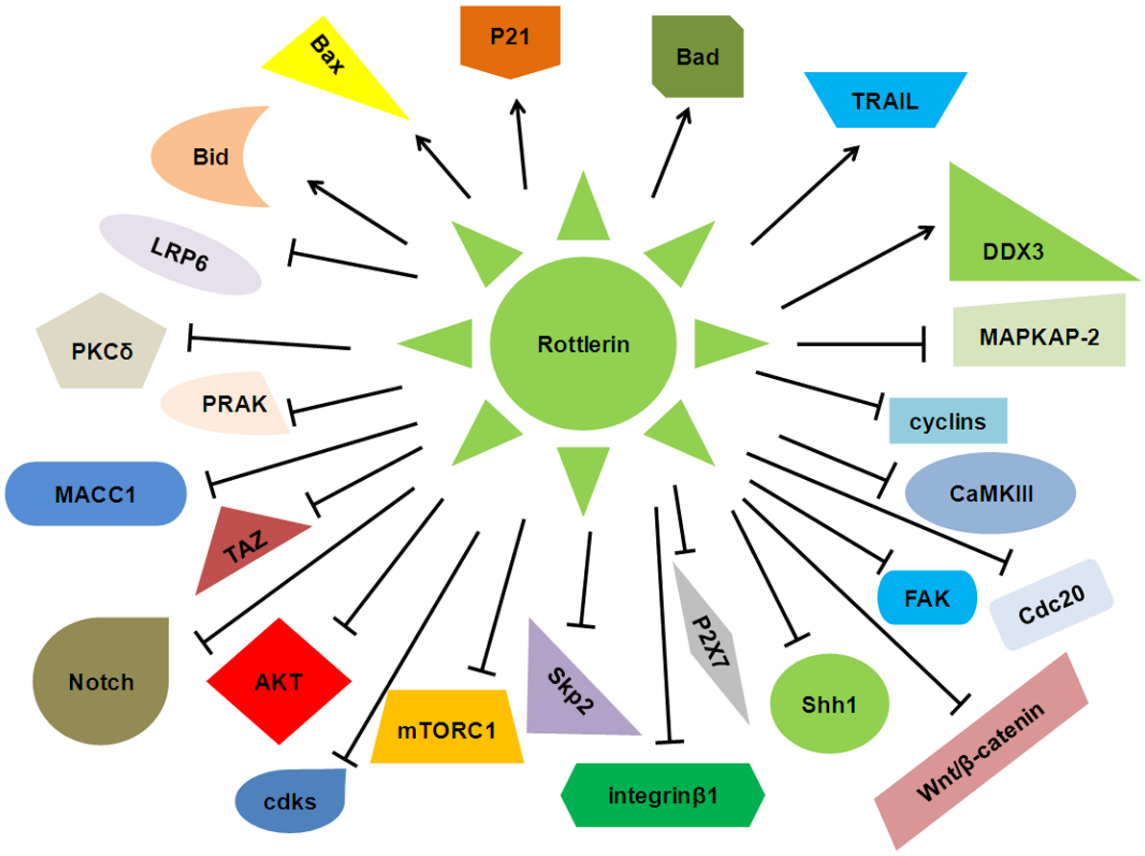

Figure 2. Illustration of rottlerin-regulated targets and signaling pathways in human cancers.

targeting multiple signaling pathways (**Figure 2**). However, there are still several questions that should be addressed. Does rottlerin exhibit its anti-tumor activity in vivo using different animal models? Is rottlerin absolutely safe for use in human? Does rottlerin have side-effects in clinical trial? Is rottlerin easy to deliver to specific organs with cancers? Without a doubt, deeper investigation is necessary to answer these questions raised by rottlerin treatment. We hope our article could stimulate the researchers to further exploit the mechanisms and potential use of rottlerin for the treatment of human cancers in the future.

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Disclosure of conflict of interest

None.

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References

[1] Salarinia R, Sahebkar A, Peyvandi M, Mirzaei HR, Jaafari MR, Riahi MM, Ebrahimnejad H, Nahand JS, Hadjati J, Asrami MO, Fadaei S, Salehi R and Mirzaei H. Epi-drugs and Epi-miRs: moving beyond current cancer therapies. Curr Cancer Drug Targets 2016; 16: 773-788.

[2] Newman DJ, Cragg GM and Snader KM. Natural products as sources of new drugs over the period 1981-2002. J Nat Prod 2003; 66: 1022-1037.

[3] Gangwar M, Goel RK and Nath G. Mallotus philippinensis muell. Arg (Euphorbiaceae): eth-

nopharmacology and phytochemistry review. Biomed Res Int 2014; 2014: 213973.
[4] Maioli E, Torricelli C and Valacchi G. Rottlerin and curcumin: a comparative analysis. Ann N Y Acad Sci 2012; 1259: 65-76.
[5] Gschwendt M, Muller HJ, Kielbassa K, Zang R, Kittstein W, Rincke G and Marks F. Rottlerin, a novel protein kinase inhibitor. Biochem Biophys Res Commun 1994; 199: 93-98.
[6] Singh R, Singhal KC and Khan NU. Antifilarial activity of mallotus philippensis lam. on setaria cervie (nematoda: filarioidea) in vitro. Indian J Physiol Pharmacol 1997; 41: 397-403.
[7] Kumar VP, Chauhan NS, Padh H and Rajani M. Search for antibacterial and antifungal agents from selected Indian medicinal plants. J Ethnopharmacol 2006; 107: 182-188.
[8] Soltoff SP. Rottlerin is a mitochondrial uncoupler that decreases cellular ATP levels and indirectly blocks protein kinase Cdelta tyrosine phosphorylation. J Biol Chem 2001; 276: 37986-37992.
[9] Zhu Y, Wang M, Zhao X, Zhang L, Wu Y, Wang B and Hu W. Rottlerin as a novel chemotherapy agent for adrenocortical carcinoma. Oncotarget 2017; 8: 22825-22834.
[10] Maioli E, Daveri E, Maellaro E, Ietta F, Cresti L and Valacchi G. Non-conventional rottlerin anticancer properties. Arch Biochem Biophys 2018; 645: 50-53.
[11] Misuth M, Horvath D, Miskovsky P and Huntosova V. Synergism between PKCdelta regulators hypericin and rottlerin enhances apoptosis in U87 MG glioma cells after light stimulation. Photodiagnosis Photodyn Ther 2017; 18: 267-274.
[12] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68: 7-30.
[13] Molina JR, Yang P, Cassivi SD, Schild SE and Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008; 83: 584-594.
[14] Brundage MD, Davies D and Mackillop WJ. Prognostic factors in non-small cell lung cancer: a decade of progress. Chest 2002; 122: 1037-1057.
[15] Liu Y, Guyton KZ, Gorospe M, Xu Q, Lee JC and Holbrook NJ. Differential activation of ERK, JNK/SAPK and P38/CSBP/RK map kinase family members during the cellular response to arsenite. Free Radic Biol Med 1996; 21: 771-781.
[16] Raingeaud J, Gupta S, Rogers JS, Dickens M, Han J, Ulevitch RJ and Davis RJ. Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. J Biol Chem 1995; 270: 7420-7426.
[17] Yeh FT, Wu CH and Lee HZ. Signaling pathway for aloe-emodin-induced apoptosis in human H460 lung nonsmall carcinoma cell. Int J Cancer 2003; 106: 26-33.
[18] You BJ, Wu YC, Bao BY, Wu CY, Yang YW, Chang YH and Lee HZ. Rottlerin inhibits lonicera japonica-induced photokilling in human lung cancer cells through cytoskeleton-related signaling cascade. Evid Based Complement Alternat Med 2011; 2011: 193842.
[19] Barron DA and Kagey JD. The role of the Hippo pathway in human disease and tumorigenesis. Clin Transl Med 2014; 3: 25.
[20] Cordenonsi M, Zanconato F, Azzolin L, Forcato M, Rosato A, Frasson C, Inui M, Montagner M, Parenti AR, Poletti A, Daidone MG, Dupont S, Basso G, Bicciato S and Piccolo S. The Hippo transducer TAZ confers cancer stem cell-related traits on breast cancer cells. Cell 2011; 147: 759-772.
[21] Zhao Z, Zheng N, Wang L, Hou Y, Zhou X and Wang Z. Rottlerin exhibits antitumor activity via down-regulation of TAZ in non-small cell lung cancer. Oncotarget 2017; 8: 7827-7838.
[22] Wen Y, Zhang D, Liu H, Wang F and Zhang Y. Heterogeneity in breast cancer. J Clin Invest 2015; 121: 3786.
[23] Kenny FS, Hui R, Musgrove EA, Gee JM, Blamey RW, Nicholson RI, Sutherland RL and Robertson JF. Overexpression of cyclin D1 messenger RNA predicts for poor prognosis in estrogen receptor-positive breast cancer. Clin Cancer Res 1999; 5: 2069-2076.
[24] Gillett C, Fantl V, Smith R, Fisher C, Bartek J, Dickson C, Barnes D and Peters G. Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining. Cancer Res 1994; 54: 1812-1817.
[25] Guttridge DC, Albanese C, Reuther JY, Pestell RG and Baldwin AS Jr. NF-kappaB controls cell growth and differentiation through transcriptional regulation of cyclin D1. Mol Cell Biol 1999; 19: 5785-5799.
[26] Torricelli C, Fortino V, Capurro E, Valacchi G, Pacini A, Muscettola M, Soucek K and Maioli E. Rottlerin inhibits the nuclear factor kappaB/cyclin-D1 cascade in MCF-7 breast cancer cells. Life Sci 2008; 82: 638-643.
[27] Torricelli C, Salvadori S, Valacchi G, Soucek K, Slabakova E, Muscettola M, Volpi N and Maioli E. Alternative pathways of cancer cell death by rottlerin: apoptosis versus autophagy. Evid Based Complement Alternat Med 2012; 2012: 980658.
[28] Kumar D, Shankar S and Srivastava RK. Rottlerin-induced autophagy leads to the apoptosis in breast cancer stem cells: molecular mechanisms. Mol Cancer 2013; 12: 171.

[29] Guertin DA and Sabatini DM. Defining the role of mTOR in cancer. Cancer Cell 2007; 12: 9-22.
[30] Garcia JA and Danielpour D. Mammalian target of rapamycin inhibition as a therapeutic strategy in the management of urologic malignancies. Mol Cancer Ther 2008; 7: 1347-1354.
[31] Dancey J. mTOR signaling and drug development in cancer. Nat Rev Clin Oncol 2010; 7: 209-219.
[32] Lu W, Lin C and Li Y. Rottlerin induces Wnt coreceptor LRP6 degradation and suppresses both Wnt/beta-catenin and mTORC1 signaling in prostate and breast cancer cells. Cell Signal 2014; 26: 1303-1309.
[33] Wang Z, Fukushima H, Inuzuka H, Wan L, Liu P, Gao D, Sarkar FH and Wei W. Skp2 is a promising therapeutic target in breast cancer. Front Oncol 2012; 1.
[34] Yin X, Zhang Y, Su J, Hou Y, Wang L, Ye X, Zhao Z, Zhou X, Li Y and Wang Z. Rottlerin exerts its anti-tumor activity through inhibition of Skp2 in breast cancer cells. Oncotarget 2016; 7: 66512-66524.
[35] Saman DM, Lemieux AM, Nawal Lutfiyya M and Lipsky MS. A review of the current epidemiology and treatment options for prostate cancer. Dis Mon 2014; 60: 150-154.
[36] Lu Y. Transcriptionally regulated, prostate-targeted gene therapy for prostate cancer. Adv Drug Deliv Rev 2009; 61: 572-588.
[37] Stavridi F, Karapanagiotou EM and Syrigos KN. Targeted therapeutic approaches for hormone-refractory prostate cancer. Cancer Treat Rev 2010; 36: 122-130.
[38] Paule B and Brion N. [EGF receptors in urological cancer. Molecular basis and therapeutic involvements]. Ann Med Interne (Paris) 2003; 154: 448-456.
[39] Onn A, Correa AM, Gilcrease M, Isobe T, Massarelli E, Bucana CD, O'Reilly MS, Hong WK, Fidler IJ, Putnam JB and Herbst RS. Synchronous overexpression of epidermal growth factor receptor and HER2-neu protein is a predictor of poor outcome in patients with stage I non-small cell lung cancer. Clin Cancer Res 2004; 10: 136-143.
[40] Shinojima N, Tada K, Shiraishi S, Kamiryo T, Kochi M, Nakamura H, Makino K, Saya H, Hirano H, Kuratsu J, Oka K, Ishimaru Y and Ushio Y. Prognostic value of epidermal growth factor receptor in patients with glioblastoma multiforme. Cancer Res 2003; 63: 6962-6970.
[41] Wells A. Tumor invasion: role of growth factor-induced cell motility. Adv Cancer Res 2000; 78: 31-101.
[42] Kharait S, Dhir R, Lauffenburger D and Wells A. Protein kinase cdelta signaling downstream of the EGF receptor mediates migration and invasiveness of prostate cancer cells. Biochem Biophys Res Commun 2006; 343: 848-856.
[43] Pommier Y. DNA topoisomerase I inhibitors: chemistry, biology, and interfacial inhibition. Chem Rev 2009; 109: 2894-2902.
[44] Hsu JL, Ho YF, Li TK, Chen CS, Hsu LC and Guh JH. Rottlerin potentiates camptothecin-induced cytotoxicity in human hormone refractory prostate cancers through increased formation and stabilization of topoisomerase I-DNA cleavage complexes in a PKCdelta-independent pathway. Biochem Pharmacol 2012; 84: 59-67.
[45] Lum JJ, Bauer DE, Kong M, Harris MH, Li C, Lindsten T and Thompson CB. Growth factor regulation of autophagy and cell survival in the absence of apoptosis. Cell 2005; 120: 237-248.
[46] Kumar D, Shankar S and Srivastava RK. Rottlerin induces autophagy and apoptosis in prostate cancer stem cells via PI3K/Akt/mTOR signaling pathway. Cancer Lett 2014; 343: 179-189.
[47] Salem AI, Alfi M, Winslow E, Cho CS and Weber SM. Has survival following pancreaticoduodenectomy for pancreas adenocarcinoma improved over time? J Surg Oncol 2015; 112: 643-649.
[48] Gardner JD and Jensen RT. Receptors and cell activation associated with pancreatic enzyme secretion. Annu Rev Physiol 1986; 48: 103-117.
[49] Williams JA. Intracellular signaling mechanisms activated by cholecystokinin-regulating synthesis and secretion of digestive enzymes in pancreatic acinar cells. Annu Rev Physiol 2001; 63: 77-97.
[50] Jensen RT and Gardner JD. Identification and characterization of receptors for secretagogues on pancreatic acinar cells. Fed Proc 1981; 40: 2486-2496.
[51] Tapia JA, Jensen RT and Garcia-Marin LJ. Rottlerin inhibits stimulated enzymatic secretion and several intracellular signaling transduction pathways in pancreatic acinar cells by a non-PKC-delta-dependent mechanism. Biochim Biophys Acta 2006; 1763: 25-38.
[52] Ohno I, Eibl G, Odinokova I, Edderkaoui M, Damoiseaux RD, Yazbec M, Abrol R, Goddard WA 3rd, Yokosuka O, Pandol SJ and Gukovskaya AS. Rottlerin stimulates apoptosis in pancreatic cancer cells through interactions with proteins of the Bcl-2 family. Am J Physiol Gastrointest Liver Physiol 2010; 298: G63-73.
[53] Arlt A, Muerkoster SS and Schafer H. Targeting apoptosis pathways in pancreatic cancer. Cancer Lett 2013; 332: 346-358.
[54] Kennedy AL, Adams PD and Morton JP. Ras, PI3K/Akt and senescence: paradoxes provide

clues for pancreatic cancer therapy. Small GTPases 2011; 2: 264-267.
[55] Saiki S, Sasazawa Y, Imamichi Y, Kawajiri S, Fujimaki T, Tanida I, Kobayashi H, Sato F, Sato S, Ishikawa K, Imoto M and Hattori N. Caffeine induces apoptosis by enhancement of autophagy via PI3K/Akt/mTOR/p70S6K inhibition. Autophagy 2011; 7: 176-187.
[56] Singh BN, Kumar D, Shankar S and Srivastava RK. Rottlerin induces autophagy which leads to apoptotic cell death through inhibition of PI3K/Akt/mTOR pathway in human pancreatic cancer stem cells. Biochem Pharmacol 2012; 84: 1154-1163.
[57] Artavanis-Tsakonas S, Rand MD and Lake RJ. Notch signaling: cell fate control and signal integration in development. Science 1999; 284: 770-776.
[58] Saqui-Salces M and Merchant JL. Hedgehog signaling and gastrointestinal cancer. Biochim Biophys Acta 2010; 1803: 786-795.
[59] Varjosalo M, Bjorklund M, Cheng F, Syvanen H, Kivioja T, Kilpinen S, Sun Z, Kallioniemi O, Stunnenberg HG, He WW, Ojala P and Taipale J. Application of active and kinase-deficient kinome collection for identification of kinases regulating hedgehog signaling. Cell 2008; 133: 537-548.
[60] Huang M, Tang SN, Upadhyay G, Marsh JL, Jackman CP, Srivastava RK and Shankar S. Rottlerin suppresses growth of human pancreatic tumors in nude mice, and pancreatic cancer cells isolated from Kras(G12D) mice. Cancer Lett 2014; 353: 32-40.
[61] Su J, Wang L, Yin X, Zhao Z, Hou Y, Ye X, Zhou X and Wang Z. Rottlerin exhibits anti-cancer effect through inactivation of S phase kinase-associated protein 2 in pancreatic cancer cells. Am J Cancer Res 2016; 6: 2178-2191.
[62] Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017; 66: 683-691.
[63] Bahrami A, Hassanian SM, ShahidSales S, Farjami Z, Hasanzadeh M, Anvari K, Aledavood A, Maftouh M, Ferns GA, Khazaei M and Avan A. Targeting RAS signaling pathway as a potential therapeutic target in the treatment of colorectal cancer. J Cell Physiol 2018; 233: 2058-2066.
[64] Gout S and Huot J. Role of cancer microenvironment in metastasis: focus on colon cancer. Cancer Microenviron 2008; 1: 69-83.
[65] Stein U. MACC1 - a novel target for solid cancers. Expert Opin Ther Targets 2013; 17: 1039-1052.
[66] Sun DW, Zhang YY, Qi Y, Liu GQ, Chen YG, Ma J and Lv GY. Prognostic and clinicopathological significance of MACC1 expression in hepatocellular carcinoma patients: a meta-analysis. Int J Clin Exp Med 2015; 8: 4769-4777.
[67] Wu Z, Zhou R, Su Y, Sun L, Liao Y and Liao W. Prognostic value of MACC1 in digestive system neoplasms: a systematic review and meta-analysis. Biomed Res Int 2015; 2015: 252043.
[68] Wang G, Fu Z and Li D. MACC1 overexpression and survival in solid tumors: a meta-analysis. Tumour Biol 2015; 36: 1055-1065.
[69] Stein U, Walther W, Arlt F, Schwabe H, Smith J, Fichtner I, Birchmeier W and Schlag PM. MACC1, a newly identified key regulator of HGF-MET signaling, predicts colon cancer metastasis. Nat Med 2009; 15: 59-67.
[70] Juneja M, Kobelt D, Walther W, Voss C, Smith J, Specker E, Neuenschwander M, Gohlke BO, Dahlmann M, Radetzki S, Preissner R, von Kries JP, Schlag PM and Stein U. Statin and rottlerin small-molecule inhibitors restrict colon cancer progression and metastasis via MACC1. PLoS Biol 2017; 15: e2000784.
[71] Tillman DM, Izeradjene K, Szucs KS, Douglas L and Houghton JA. Rottlerin sensitizes colon carcinoma cells to tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis via uncoupling of the mitochondria independent of protein kinase C. Cancer Res 2003; 63: 5118-5125.
[72] Banno T, Gazel A and Blumenberg M. Pathway-specific profiling identifies the NF-kappa B-dependent tumor necrosis factor alpha-regulated genes in epidermal keratinocytes. J Biol Chem 2005; 280: 18973-18980.
[73] Maioli E, Greci L, Soucek K, Hyzdalova M, Pecorelli A, Fortino V and Valacchi G. Rottlerin inhibits ROS formation and prevents NFkappaB activation in MCF-7 and HT-29 cells. J Biomed Biotechnol 2009; 2009: 742936.
[74] Berretta M, Cavaliere C, Alessandrini L, Stanzione B, Facchini G, Balestreri L, Perin T and Canzonieri V. Serum and tissue markers in hepatocellular carcinoma and cholangiocarcinoma: clinical and prognostic implications. Oncotarget 2017; 8: 14192-14220.
[75] Sherman M. Hepatocellular carcinoma: epidemiology, surveillance, and diagnosis. Semin Liver Dis 2010; 30: 3-16.
[76] Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006; 295: 65-73.
[77] Wilky BA, Kim C, McCarty G, Montgomery EA, Kammers K, DeVine LR, Cole RN, Raman V and Loeb DM. RNA helicase DDX3: a novel therapeutic target in Ewing sarcoma. Oncogene 2016; 35: 2574-2583.
[78] Wang Z, Shen GH, Xie JM, Li B and Gao QG. Rottlerin upregulates DDX3 expression in he-

patocellular carcinoma. Biochem Biophys Res Commun 2018; 495: 1503-1509.
[79] Shi J, Ning H, He G, Huang Y, Wu Z, Jin L and Jiang X. Rottlerin inhibits cell growth, induces apoptosis and cell cycle arrest, and inhibits cell invasion in human hepatocellular carcinoma. Mol Med Rep 2018; 17: 459-464.
[80] Aibaidula A, Lu JF, Wu JS, Zou HJ, Chen H, Wang YQ, Qin ZY, Yao Y, Gong Y, Che XM, Zhong P, Li SQ, Bao WM, Mao Y and Zhou LF. Establishment and maintenance of a standardized glioma tissue bank: Huashan experience. Cell Tissue Bank 2015; 16: 271-281.
[81] DeAngelis LM. Brain tumors. N Engl J Med 2001; 344: 114-123.
[82] Hanahan D and Weinberg RA. The hallmarks of cancer. Cell 2000; 100: 57-70.
[83] Hunter T. Oncoprotein networks. Cell 1997; 88: 333-346.
[84] Nishizuka Y. The role of protein kinase C in cell surface signal transduction and tumour promotion. Nature 1984; 308: 693-698.
[85] Nishizuka Y. The molecular heterogeneity of protein kinase C and its implications for cellular regulation. Nature 1988; 334: 661-665.
[86] Nishizuka Y. Intracellular signaling by hydrolysis of phospholipids and activation of protein kinase C. Science 1992; 258: 607-614.
[87] Edwards AS and Newton AC. Phosphorylation at conserved carboxyl-terminal hydrophobic motif regulates the catalytic and regulatory domains of protein kinase C. J Biol Chem 1997; 272: 18382-18390.
[88] Schonwasser DC, Marais RM, Marshall CJ and Parker PJ. Activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway by conventional, novel, and atypical protein kinase C isotypes. Mol Cell Biol 1998; 18: 790-798.
[89] Jane EP, Premkumar DR and Pollack IF. Coadministration of sorafenib with rottlerin potently inhibits cell proliferation and migration in human malignant glioma cells. J Pharmacol Exp Ther 2006; 319: 1070-1080.
[90] Xie Q, Wu Q, Mack SC, Yang K, Kim L, Hubert CG, Flavahan WA, Chu C, Bao S and Rich JN. CDC20 maintains tumor initiating cells. Oncotarget 2015; 6: 13241-13254.
[91] Wang L, Hou Y, Yin X, Su J, Zhao Z, Ye X, Zhou X, Zhou L and Wang Z. Rottlerin inhibits cell growth and invasion via down-regulation of Cdc20 in glioma cells. Oncotarget 2016; 7: 69770-69782.
[92] Leiter U, Eigentler T and Garbe C. Epidemiology of skin cancer. Adv Exp Med Biol 2014; 810: 120-140.
[93] Berwick M, Buller DB, Cust A, Gallagher R, Lee TK, Meyskens F, Pandey S, Thomas NE, Veierod MB and Ward S. Melanoma epidemiology and prevention. Cancer Treat Res 2016; 167: 17-49.
[94] Testori A, Ribero S and Bataille V. Diagnosis and treatment of in-transit melanoma metastases. Eur J Surg Oncol 2017; 43: 544-560.
[95] Daveri E, Valacchi G, Romagnoli R, Maellaro E and Maioli E. Antiproliferative effect of rottlerin on Sk-Mel-28 melanoma cells. Evid Based Complement Alternat Med 2015; 2015: 545838.
[96] Assouline S, Culjkovic B, Cocolakis E, Rousseau C, Beslu N, Amri A, Caplan S, Leber B, Roy DC, Miller WH Jr and Borden KL. Molecular targeting of the oncogene eIF4E in acute myeloid leukemia (AML): a proof-of-principle clinical trial with ribavirin. Blood 2009; 114: 257-260.
[97] Ko SY, Guo H, Barengo N and Naora H. Inhibition of ovarian cancer growth by a tumor-targeting peptide that binds eukaryotic translation initiation factor 4E. Clin Cancer Res 2009; 15: 4336-4347.
[98] Lin CJ, Sukarieh R and Pelletier J. Silibinin inhibits translation initiation: implications for anticancer therapy. Mol Cancer Ther 2009; 8: 1606-1612.
[99] Daveri E, Maellaro E, Valacchi G, Ietta F, Muscettola M and Maioli E. Inhibitions of mTORC1 and 4EBP-1 are key events orchestrated by Rottlerin in SK-Mel-28 cell killing. Cancer Lett 2016; 380: 106-113.
[100] Basu A, Adkins B and Basu C. Down-regulation of caspase-2 by rottlerin via protein kinase C-delta-independent pathway. Cancer Res 2008; 68: 2795-2802.
[101] Mertens-Walker I, Bolitho C, Baxter RC and Marsh DJ. Gonadotropin-induced ovarian cancer cell migration and proliferation require extracellular signal-regulated kinase 1/2 activation regulated by calcium and protein kinase C{delta}. Endocr Relat Cancer 2010; 17: 335-349.
[102] Prudnikova TY and Chernoff J. The Group I Pak inhibitor Frax-1036 sensitizes 11q13-amplified ovarian cancer cells to the cytotoxic effects of Rottlerin. Small GTPases 2017; 8: 193-198.
[103] Qi P, He Z, Zhang L, Fan Y and Wang Z. Rottlerin-induced autophagy leads to apoptosis in bladder cancer cells. Oncol Lett 2016; 12: 4577-4583.
[104] Davies L and Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006; 295: 2164-2167.
[105] Crile G Jr, Pontius KI and Hawk WA. Factors influencing the survival of patients with follicular carcinoma of the thyroid gland. Surg Gynecol Obstet 1985; 160: 409-413.
[106] Lin CJ, Lin CY, Chen Y, Huang SH and Wang SM. Rottlerin inhibits migration of follicular thy-

roid carcinoma cells by PKCdelta-independent destabilization of the focal adhesion complex. J Cell Biochem 2010; 110: 428-437.
[107] Hou Y, Feng S, Wang L, Zhao Z, Su J, Yin X, Zheng N, Zhou X, Xia J and Wang Z. Inhibition of Notch-1 pathway is involved in rottlerin-induced tumor suppressive function in nasopharyngeal carcinoma cells. Oncotarget 2017; 8: 62120-62130.
[108] Ringshausen I, Schneller F, Bogner C, Hipp S, Duyster J, Peschel C and Decker T. Constitutively activated phosphatidylinositol-3 kinase (PI-3K) is involved in the defect of apoptosis in B-CLL: association with protein kinase Cdelta. Blood 2002; 100: 3741-3748.
[109] Ringshausen I, Oelsner M, Weick K, Bogner C, Peschel C and Decker T. Mechanisms of apoptosis-induction by rottlerin: therapeutic implications for B-CLL. Leukemia 2006; 20: 514-520.
[110] Shemon AN, Sluyter R and Wiley JS. Rottlerin inhibits P2X(7) receptor-stimulated phospholipase D activity in chronic lymphocytic leukaemia B-lymphocytes. Immunol Cell Biol 2007; 85: 68-72.
[111] Lounasmaa M, Widén CJ, Tuuf CM and Huhtikangas A. On the phloroglucinol derivatives of mallotus philippinensis. Planta Medica 1975; 28: 16.