
mTOR Inhibitory Activities of Natural Phytochemicals

Heng Kean Tan¹, Ahmed Ismail Hassan Moad², Mei Lan Tan¹,²*

Abstract

The mammalian target of rapamycin (mTOR) kinase plays an important role in regulating cell growth and cell cycle progression in response to cellular signals. It is a key regulator of cell proliferation and many upstream activators and downstream effectors of mTOR are known to be deregulated in various types of cancers. Since the mTOR signalling pathway is commonly activated in human cancers, many researchers are actively developing inhibitors that target key components in the pathway and some of these drugs are already on the market. Numerous preclinical investigations have also suggested that some herbs and natural phytochemicals, such as curcumin, resveratrol, timosaponin III, gallic acid, diosgenin, pomegranate, epigallocatechin gallate (EGCC), genistein and 3,3'-diindolylmethane inhibit the mTOR pathway either directly or indirectly. Some of these natural compounds are also in the clinical trial stage. In this review, the potential anti-cancer and chemopreventive activities and the current status of clinical trials of these phytochemicals are discussed.

Keywords: mTOR signalling pathway - PI3K/Akt/mTOR - natural compounds - mTOR inhibitors

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Introduction

The mammalian target of rapamycin (mTOR) kinase is a conserved serine/threonine protein kinase that plays an important role in regulating many fundamental molecules mediating cell growth and cell cycle progression in response to cellular signals in eukaryotes (Liu et al., 2009b; Houghton, 2010). The mTOR signalling pathway has a central role in cellular processes such as cell survival, cell growth and proliferation, cell death, and tumor angiogenesis. This pathway is frequently hyper-activated in several human malignancies and therefore is considered to be an interesting and attractive therapeutic target for anti-cancer therapy.

The mTOR is also known as FKBP12-rapamycin associated protein (FRAP), or rapamycin and FKBP12 target (RAFT), or rapamycin target (RAPT), or sirolimus effector protein (SEP). The mTOR gene is located on human chromosome 1 in location 1p36.2 (Huang and Houghton, 2003). It is identified in mammalian cells as a 289 kDa serine/threonine kinase consisting of 2549 amino acids and the structural domains of mTOR, are evolutionarily conserved, comprising of six functional domains (Sabatini et al., 1994; Sabers et al., 1995; Abraham, 1998). The domains comprise of (1) HEAT (Huntingtin elongation factor 3, a subunit of protein phosphatase 2A and TOR1) domain, which mediates protein-protein interactions; (2) FAT (FRAP-ATM-TRAPP) domain; (3) FRB (FKBP12-rapamycin binding) domain, which mediates the inhibitory action of rapamycin on Raptor-bound mTOR; (4) PIKK (PI3-kinase-related kinase) domain, serine phosphorylation sites (S2035 and S2481); (5) RD (Repressor domain); and (6) the carboxy-terminal FATC domain (Kirken and Wang, 2003; Asnaghi et al., 2004).

The mTOR kinase plays a crucial role in regulating cell growth, cell proliferation, cell survival, protein synthesis and autophagy. It regulates and controls the transcription of ribosomal proteins and the synthesis of rRNA and tRNA (Hardwick et al., 1999; Powers and Walter, 1999). In general, the activity of mTOR is regulated by insulin and other growth factors via the phosphatidylinositol 3-kinase (PI3K)–Akt pathway (Kadowaki and Kanazawa, 2003). In eukaryotic cells, mTOR exists as two different complexes: mTORC1; a rapamycin-sensitive complex defined by its interaction with Raptor (regulatory-associated protein of mTOR) and mTORC2; a rapamycin-insensitive complex defined by its interaction with Rictor (rapamycin-insensitive companion of mTOR) (Bharti and Aggarwal, 2002; Loewith et al., 2002; Sarbassov et al., 2004). Raptor is the first protein shown to bind directly to mTOR that is required to mediate mTOR regulation of p70 ribosomal S6 kinase (p70S6K) and the binding protein of eukaryotic translation initiation factor 4E (eIF4E) (4E-BP1) activities (Bharti and Aggarwal, 2002; Kim et al., 2002a). On the other hand, PRAS40 and Deptor are identified as...
distinct negative regulators of mTORC1 (Sancak et al., 2007; Peterson et al., 2009).

In the rapamycin-sensitive mTOR signalling pathway, rapamycin binds to FK506-binding protein of 12 kDa (FKBP12), and subsequently, the complex binds to the FRB domain of mTORC1. This weakens the interaction between mTOR and Raptor and subsequently inhibits the mTORC1 functions (Kirk and Wang, 2003; Guertin et al., 2004; Hay and Sonenberg, 2004). However, the mechanisms on how rapamycin and several rapamycin derivatives bind to FKBP12 to inhibit mTORC1 signalling remain poorly defined (Dowling et al., 2010). Starvation or lack of nutrients such as amino acids and/or glucose appears to mimic rapamycin treatment which causes rapid inactivation of p70S6K and hypophosphorylation of the 4E-BP1 (Proud, 2002).

The activity of mTOR is regulated by various growth factors such as insulin, insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and platelet-derived growth factor (PDGF) (Gomez-Pinillos and Ferrari, 2012). Growth factor-induced activation of mTOR is mediated by Class I PI3K which has the unique ability to generate oncogenic phosphatidylinositol-3,4,5-triphosphate (PIP3). Class II and Class III PI3Ks lack this ability and therefore have not been linked to cancer (Vogt et al., 2010). Class I PI3Ks are further divided into Class IA PI3Ks and Class IB PI3K. Class IA PI3Ks are heterodimers consisting of a p85 regulatory subunit that associates with p110α, β or δ catalytic subunit and are involved primarily in the pathogenesis of human cancer (Rodon et al., 2013).

Following growth factor binding to its cognate receptor tyrosine kinase (RTK), Class IA PI3Ks are recruited to the cell membrane by direct interaction of the p85 subunit with the activated receptors or by interaction with adaptor proteins associated with the receptors. Binding removes the inhibitory effect of p85 on p110, resulting in activation of p110 catalytic subunit. The activated p110 subunit catalyses the phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to PIP3 at the membrane. PIP3 is an important second messenger in the cell and is the predominant mediator of PI3K activity. PIP3 acts as docking sites for signalling proteins that have pleckstrin homology (PH) domain, including Akt and 3-phosphoinositide-dependent kinase 1 (PDK1) (Vogt et al., 2010; Baselga, 2011). Figure 1 illustrates the mTOR signalling pathway in general.

The serine/threonine protein kinase Akt, also known as protein kinase B (PKB), a downstream effector of PI3K, is a critical mediator of mTOR activity (Hay and Sonenberg, 2004). Akt activation is initiated by translocation to the plasma membrane, which is mediated by docking of Akt to PIP3 on the membrane. Akt is then phosphorylated on Thr308 by PDK1 and on Ser473 by putative PDK2. A number of potential PDK2s have been identified, including integrin-linked kinase (ILK), protein kinase C β2, DNA-dependent protein kinase (DNA-PK), ataxia telangiectasia mutated (ATM), Akt itself and mTORC2. Both phosphorylation events are required for full activation of Akt. Once Akt has been phosphorylated and activated, it phosphorylates many other proteins, thereby regulating a wide range of cellular processes involved in protein synthesis, cell survival, proliferation and metabolism. Akt activates mTOR either by direct phosphorylation of mTOR at Ser2448 (Nave et al., 1999) or by indirect phosphorylation and inhibition of tuberous sclerosis complex 2 (TSC2) (Inoki et al., 2002). Akt phosphorylation of TSC2 represses GTPase-activating protein (GAP) activity, thereby allowing GTP-bound

Figure 1. The mTOR Signalling Pathway and Regulatory Feedback Loop

active Ras homolog enriched in brain (Rheb) to activate mTOR (Plas and Thompson, 2005). Phosphorylation of mTOR at Ser2481 (an autophosphorylation site) correlates to the activation of mTOR catalytic activity (Caron et al., 2010; Soliman et al., 2010).

When conditions are favourable for cell growth, activated mTORC1 phosphorylates several substrates to promote anabolic processes (such as ribosome biogenesis, translation and the synthesis of lipids and nucleotides) and suppress catabolic processes (such as autophagy) (Fruman and Rommel, 2014). The mTORC1 regulates protein synthesis through the phosphorylation and inactivation of the repressor of mRNA translation, 4E-BP1 and through the phosphorylation and activation of p70S6K. Phosphorylation of 4E-BP1 releases eukaryotic translation initiation factor 4E (eIF4E), allowing it to interact with eIF4G to initiate cap-dependent translation. Activated p70S6K regulates cell growth via increased translation of 5’TOP (terminal oligopyrimidine tract) mRNAs, which encode components of the translation machinery, such as ribosomal proteins and elongation factors. Through the phosphorylation of several other effectors, mTORC1 promotes lipid biogenesis and metabolism, and suppresses autophagy (Hay and Sonenberg, 2004; Gomez-Pinillos and Ferrari, 2012; Laplante and Sabatini, 2013). In contrast, mTORC2 does not have direct role in regulating protein translation. However, mTORC2 is found to phosphorylate serum and glucocorticoid-regulated kinase 1 (SGK1), protein kinase C (PKC), and also Akt at Ser473, which in turn regulates cell cycle progression, cell survival, metabolism and cytoskeletal organization (Gomez-Pinillos and Ferrari, 2012; Laplante and Sabatini, 2012).

The tumour suppressor suppressor of tumorigenicity and tensin homolog deleted on chromosome 10 (PTEN) is the most important negative regulator of the PI3K signalling pathway. PTEN is a phosphatidylinositol-3-phosphate that antagonizes PI3K activity by dephosphorylating PIP3 that is generated by PI3K (Abdulkareem and Blair, 2013). Loss of PTEN results in an unrestrained signalling of the PI3K pathway, leading to the formation of cancer. It is also associated with many types of cancers, including breast cancer (Vivancos and Sawyers, 2002; Sansal and Sellers, 2004). Another important protein involved in the regulation of mTORC1 activity is the tuberous sclerosis complex (TSC), which is a heterodimer of two proteins, TSC1 (also known as hamartin) and TSC2 (also known as tuberin) (Hay and Sonenberg, 2004). TSC1 and TSC2 functions as a GAP that negatively regulates a small GTPase called Rheb, transforming Rheb into its inactive GDP-bound state which subsequently unable to activate mTOR (Hay and Sonenberg, 2004). Finally, regulatory feedback loop exists as an intrinsic mechanism of self-control to refrain further activation of mTOR pathway. Following mTOR phosphorylation, activated p70S6K phosphorylates and destabilizes insulin receptor substrate 1 (IRS1), thereby inhibiting PI3K activation and blocking upstream overstimulation of the PI3K/Akt/mTOR cascade (Gomez-Pinillos and Ferrari, 2012; Shimobayashi and Hall, 2014) (Figure 1).

One of most studied and important pathways involved in the regulation of autophagy is the PI3K/Akt/mTOR signalling pathway. Inhibition of mTOR by nutrient-depletion, starvation or rapamycin leads to the induction of autophagy. Increased levels of the mTOR kinase are found to inhibit the autophagy process, resulting in excessive cell growth and tumor development. Studies have shown that mTORC1 controls autophagy through the regulation of a protein complex composed of ULK1 (unc-51-like kinases), mAtg13 and FIP200 (Ganley et al., 2009; Hosokawa et al., 2009; Jung et al., 2009). ULK kinase complex is directly controlled by mTOR, of which maintains the hyperphosphorylation state of mAtg13 and suppresses the induction of autophagy (Galluzzi et al., 2008). Inhibition of mTOR by rapamycin leads to dephosphorylation of ULK1, ULK2, and mAtg13 and activates ULK to phosphorylate FIP200, which suggests that ULK-Atg13-FIP200 complexes are direct targets of mTOR and important regulators of autophagy in response to mTOR signalling (Jung et al., 2009).

In contrast to mTORC1, relatively little is known regarding the regulatory pathway of mTORC2. The mTOR-Rictor complex, unlike mTOR-Raptor, does not bind to FRB domain and is insensitive to rapamycin treatment (Loewi et al., 2002; Sarbassov et al., 2004). The mTORC2 complex promotes cell signalling through phosphorylation and activation of the pro-survival and pro-proliferative kinase Akt, which positively regulates cell survival, proliferation and metabolism (Sarbassov et al., 2006; Manning and Cantley, 2007). The molecular mechanism by which mTORC2 regulates cytoskeletal organization has not been clearly defined, although many different studies have reported that knocking down mTORC2 components affects actin polymerization and disrupts cell morphology (Jacinto et al., 2004; Sarbassov et al., 2004). In another study, depletion of mTOR and Rictor, but not Raptor, impairs actin polymerization in neutrophils stimulated with chemoattractants and that small Rho GTPases Rac and Cdc42 serve as downstream effectors of Rictor to regulate actin assembly and organization in neutrophils (He et al., 2013).

The mTOR Signalling Pathway and Cancer

The mTOR pathway is a key regulator of cell proliferation and several upstream activators and downstream effectors of mTOR are known to be deregulated in some cancers such as renal cell carcinoma, non-small cell lung cancer, breast cancer, sarcomas, colorectal and gastrointestinal tumors (Law, 2005; Tokunaga et al., 2008; Li et al., 2013; Takahashi et al., 2014; Wang and Zhang, 2014). The mTOR signalling is constitutively activated in many tumor types, suggesting that mTOR is an attractive target for cancer drug development and therapy (Yu et al., 2001; Chan, 2004; Shor et al., 2009; Han et al., 2013; Pandurangan, 2013). The mTOR signalling network consists of a number of tumor suppressor genes and proto-oncogenes, thereby explains that aberrant activities of these genes will promote the formation of cancerous cells.

The signalling network defined by PI3K, Akt and mTOR controls most hallmarks of cancer, including cell cycle, survival, metabolism, motility and genomic
in vitro amplification or overexpression of PDK1 was found in mice, indicating that Akt1 accelerates carcinogen-induced DMBA in the transgenic mice, especially in post-lactation susceptibility of forming mammary tumors induced by mammary glands alone did not increase the frequency of promoter revealed that expression of myristoylated-Akt1 (myr-Akt1) under the control of the MMTV-LTR transgenic mice generated by expressing myristoylated Akt is frequently and constitutively active in many types of human cancer. Constitutive Akt activation can occur as a result of amplification of Akt genes or due to mutations in components of the signalling pathway that activate Akt. Constitutive Akt signalling is believed to promote proliferation and increase cell survival, thereby contributing to cancer progression (Nicholson and Anderson, 2002). Amplification of Akt1, Akt2 and Akt3 has been reported in breast, endometrium and large intestine cancers, 30% of glioblastomas and spinal tumors, and less commonly in cancers of the prostate, bladder, adrenal glands, thyroid, breast, skin (melanomas) and colon (Abdulkareem and Blair, 2013).

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Aberrant activation of mTOR has been implicated in certain cancers. Activation of mTOR provides tumour cells with a growth advantage by promoting protein synthesis and contributes to the genesis of cancer through its effect on cell cycle progression (Fingar et al., 2004). The effects of mTOR on cell cycle progression is mediated, at least in part, by the increased translation of positive regulators of cell cycle progression, such as cyclin D1 and Myc, and by decreased translation of negative regulators thereof, such as p27kip1 (Gera et al., 2004; Hay and Sonenberg, 2004). On the other hand, tumor suppressor PTEN is frequently mutated in advanced stages of human cancers, particularly glioblastoma, endometrial and prostate cancers. Germline mutations in the PTEN gene give rise to Cowden’s disease, which is associated with an increased risk of developing breast cancer and other cancers (Nicholson and Anderson, 2002). Somatic loss of PTEN by gene mutation or deletion frequently occurs in human cancers. PTEN is deleted or mutated in approximately 45% of uterine endometrial cancers, 30% of glioblastomas and spinal tumors, and less commonly in cancers of the prostate, bladder, adrenal glands, thyroid, breast, skin (melanomas) and colon (Abdulkareem and Blair, 2013).

Clinical Development of PI3K/Akt/mTOR (PAM) Inhibitors

Since mTOR signalling pathway is one of the most commonly activated signalling networks in human cancers and that kinases are amenable to pharmacological intervention, many pharmaceutical companies and academic laboratories are actively developing inhibitors that target key components in the pathway (Moschetta et al., 2014). Many of the agents developed and evaluated in early stage clinical trials have been shown to be safe, well tolerated and effective in multiple tumor types. Current PAM inhibitors in early development include reversible ATP-competitive inhibitors of the four p110 isoforms of Class I PI3K (also known as pan-PI3K inhibitors), the irreversible pan-PI3K inhibitors, p110 isoform-specific inhibitors, dual pan-PI3K-mTOR inhibitors, Akt inhibitors and mTOR inhibitors (Rodon et al., 2013; Porta et al., 2014).

Wortmannin and LY294002 are two well known, first generation pan-PI3K inhibitors. Wortmannin and LY294002 are effective inhibitors of PI3K and have shown anti-proliferative and apoptotic effects in vitro and in vivo. However, the use of these two compounds is limited to the preclinical level due to their instability in aqueous solutions, toxic side effects, poor pharmaceutical properties and lack of selectivity for individual PI3K p110 isoforms (Pal and Mandal, 2012). Isoform-specific inhibitors are of particular interest because agents that target single isoform may produce fewer side effects and less toxicity to the immune system due to the fact that p110α and p110β play important roles in multiple cellular processes while p110γ and δ isoforms are important in the immune system. Some inhibitors of Akt are being tested clinically, although the development of Akt-specific and isozyme-selective inhibitors was predicted to be difficult due to high degree of homology in the ATP binding pocket
Rapamycin, also known as sirolimus, is a prototypical mTOR inhibitor. It is an antibiotic macrolide derived from bacterium *Streptomyces hygroscopius*, and first isolated in 1975 (Sehgal et al., 1975; Vezina et al., 1975). Rapamycin was first developed as immunosuppressant by Wyeth pharmaceutical company in 1997 and more recently presented as anti-cancer agents in the form of various analogues (Liu et al., 2009b). Rapamycin binds to its intracellular receptor FKBP12, and subsequently attaches to the mTORC1 and suppresses mTOR-mediated phosphorylation of p70S6K and 4E-BP1. Rapamycin has been precluded from clinical development due to its poor aqueous solubility and chemical instability (Hidalgo and Rowinsky, 2000; Mita et al., 2003). Rapamycin analogues (also known as rapalogues) inhibit mTOR through the same mechanism as rapamycin, but have better pharmacological properties for clinical use in cancer. In general, the therapeutic effects of rapamycin analogues are similar to rapamycin (Tsang et al., 2007). Rapamycin analogues with improved stability and pharmacological properties have been significantly tolerated by patients in Phase I trials, and the agents have shown promising antitumor effect in many types of cancers including breast cancer (Noh et al., 2004).

Temsirolimus (CCI-779) and everolimus (RAD001) are two rapamycin analogues that have been developed as anti-cancer drugs (Hasskarl, 2014). Temsirolimus is the first mTOR inhibitor approved by FDA, USA for the treatment of advanced renal cell carcinoma in 2007. This is followed by the approval of everolimus for the treatment of adults with advanced and recurrent renal cell carcinoma (2009); adults with progressive neuroendocrine tumors of pancreatic origin (2011); adults with tuberous sclerosis complex (TSC) who have renal angiomyolipomas not requiring immediate surgery (2012); children with TSC who have a rare brain tumor called subependymal giant cell astrocytoma (2012); and for use in combination with exemestane to treat certain postmenopausal women with advanced hormone receptor positive, HER2-negative breast cancer (2012) (Hasskarl, 2014). Nevertheless, rapalogues are not broadly effective as single agents, although they have been approved for the treatment of a few tumour types for which modest therapeutic effects can be achieved (Fruman and Rommel, 2014). Preclinical studies demonstrated that Akt activation was triggered after blockade of mTORC1 by rapamycin and rapalogues (Sun et al., 2005; O’Reilly et al., 2006; Wan et al., 2007). Clinically, upon mTOR blockade with everolimus, Akt phosphorylation was upregulated in 50% of the treated tumors (Tabernero et al., 2008). The increased Akt activity can ultimately enhance tumour growth. This limited anti-tumour activity of mTOR inhibitors is suspected to be related to the fact that these agents only inhibit the mTORC1 complex. The blockade of mTOR and the resulting inhibition of p70S6K relieves regulatory feedback loop, which results in IGF-1R-mediated feedback activation of Akt (Baselga, 2011; Rodon et al., 2013). Therefore, agents targeting both mTORC1 and mTORC2, and dual pan-class I PI3K-mTOR inhibitors are being developed (Rodon et al., 2013).

In addition, preclinical models have shown that combining mTOR inhibitors and IGF-1R antibodies/inhibitors result in blockage of mTOR inhibitor-induced Akt activation (Wan et al., 2007), and this combination is currently being explored in clinical trials (Chen and Sharon, 2013). In the pre-clinical and clinical studies, the inhibitors targeting the different members of mTOR pathway have been used alone or in combination with other targeted agents for the treatment of breast cancer (Ghayad and Cohen, 2010).

Although the mTOR-targeting therapy was based on the premise that an essential PI3K effector Akt activates the rapamycin-sensitive mTORC1 pathway, new data suggests that rapamycin-insensitive mTORC2 phosphorylates Akt on a key activation site, providing some knowledge that the relationship between mTOR and PI3K signalling is complex (Guerin and Sabatini, 2009). Inhibitors that target both mTORC1 and mTORC2 would be expected to block activation of the PI3K pathway more effectively than rapamycin and its analogues (Liu et al., 2009b). Current evidences from the analyses of some solid tumors also suggests that dual PI3K/mTOR inhibitors, which bind to and inactivate both PI3K and mTOR, may achieve better outcomes among resistant cancers (Tang and Ling, 2014). Currently, OSI-027 (OSI Pharmaceuticals, USA), AZD8055 (Astra Zeneca, UK), and INK128 (Intellikine, USA) are the first three ATP-competitive mTOR inhibitors to enter clinical trials in patients with advanced solid tumors and lymphoma (Liu et al., 2009a; Garcia-Echeverria, 2010; Houghton, 2010). OSI-027 is the first orally bioavailable small-molecule mTORC1/mTORC2 inhibitor, a semi-synthetic compound with the ability of eliciting both tumor cell apoptosis and autophagy and halting tumor cell proliferation (Yap et al., 2008; Vakana et al., 2010).

**Natural Phytochemicals as mTOR Inhibitors**

Numerous important anticancer drugs in the market are either obtained from natural sources, by structural modification of natural compounds, or by synthesis of new compounds using natural compound as lead (Cragg et al., 1997; da Rocha et al., 2001). Therefore, sourcing out new drugs and the continuous interest in using natural compounds for cancer therapy is a global effort. Numerous preclinical investigations have shown that some herbs and natural phytochemicals, such as curcumin, resveratrol, timosaponin III, gallic acid, diosgenin, pomegranate, epigallocatechin gallate (EGCC), genistein, and 3,3’-diindolylmethane inhibit mTOR pathway either directly or indirectly (Table 1). Some of them are undergoing clinical trials as chemotherapeutic agents, chemopreventive compounds and/or combination therapy to improve the efficacy of the standard chemotherapy. These natural phytochemicals with mTOR inhibitory activities have great potential in cancer prevention. This is in view that higher consumption of fruits and vegetables was associated with lower risk of cancer (Gullett et al., 2010).

Curcumin, a polyphenol natural compound extracted from the plant *Curcuma longa* L., is commonly used
as spice in India and Southeast Asia. It is used as food additive and traditional Indian medicine for the treatment of various diseases such as biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis (Shishodia et al., 2007). Curcumin has shown exceptional chemopreventive and anti-tumor activities in some pre-clinical studies. In HCT116 colorectal cancer cells, curcumin downregulates protein and mRNA expression of mTOR, Raptor and Rictor, suggesting that curcumin exerts its anti-proliferative effects by inhibiting the mTOR signalling pathway and thus may represent a novel class of mTOR inhibitor (Johnson et al., 2009). In human Rh1 and Rh30 rhabdomyosarcoma cells, DU145 prostate cancer cells, MCF-7 breast cancer cells and Hela cervical cancer cells, curcumin rapidly inhibits the phosphorylation of mTOR and its downstream effector molecules such as p70S6K and 4E-BP1, indicating that curcumin may execute its anticancer activity primarily by blocking mTOR-mediated signalling pathways in these tumor cells (Beevers et al., 2006). Furthermore, curcumin induces apoptosis, inhibits cell growth and inhibits the basal or type I insulin-like growth factor-induced motility of the Rh1 and Rh30 cells (Beevers et al., 2006). Curcumin is found to dissociate Raptor, at low concentration, and Rictor, at high concentration, from mTOR complex. However, it is unclear if curcumin disrupts the mTOR complex by direct binding to mTOR or to a component of the mTOR complexes (Beevers et al., 2009). In human PC3 prostate cancer cells, curcumin suppresses murine double minute 2 (MDM2) oncogene expression through the erythroidblastosis virus transcription factor 2 (EST2) by modulating PI3K/mTOR/ETS2 signalling pathway (Li et al., 2007a). In both human U87-MG and U373-MG malignant glioma cells, curcumin inhibits the Akt/mTOR/p70S6K pathway and activates the extracellular signal-regulated kinase (ERK) pathway, resulting in the induction of autophagy. On the other hand, activation of Akt pathway by recombinant full-length human active Akt1 protein (rAkt1) inhibited curcumin-induced autophagy and decreased curcumin-inhibited phosphorylation of Akt and p70S6K, suggesting that curcumin-induced inactivation of Akt/mTOR/p70S6K pathway plays a role in induction of autophagy (Aoki et al., 2007). As combined treatment, curcumin and dual PI3K/Akt and mTOR inhibitor induce apoptosis through p53-dependent Bcl-2 mRNA downregulation at the transcriptional level and Mcl-1 protein down-regulation at the post-transcriptional level in human renal carcinoma Caki cells (Seo et al., 2014).

The promising effect of curcumin at the preclinical phases has led to the initiation of several clinical trials. In Phase I clinical studies, it has been shown that curcumin is not toxic to human; and in Phase II clinical trial, curcumin is well tolerated and produces some biological activity in patients with advanced pancreatic cancer (Cheng et al., 2001; Sharma et al., 2001; Lao et al., 2006; Dhillon et al., 2008). Curcumin taken orally for 3 months produces histologic improvement of precancerous lesions in 1 out of 2 patients with recently resected bladder cancer, 2 out of 7 patients of oral leucoplaikia, 1 out of 6 patients of intestinal metaplasia of the stomach, 1 out of 4 patients with uterine cervical intraepithelial neoplasm (CIN) and 2 out of 6 patients with Bowen’s disease (Cheng et al., 2001). Radiologically stable colorectal cancer was demonstrated in 5 out of 15 patients after 2-4 months of treatment with curcuma extract at doses between 440 and 2200 mg/day, containing 36-180 mg of curcumin (Sharma et al., 2001). In a Phase II, nonrandomized, open-label clinical trial in 44 eligible smokers with eight or more aberrant crypt foci (ACF) on screening colonoscopy, a significant 40% reduction in ACF number occurred with the 4-g dose of curcumin for 30 days. The ACF reduction in the 4-g group was associated with a significant, five-fold increase in post-treatment plasma curcumin/conjugate levels (Carroll et al., 2011). A Phase II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer reported that 8 g oral curcumin daily with gemcitabine-based chemotherapy was safe and feasible in patients with pancreatic cancer (Kanai et al., 2011). However, all these are short term studies and the unremarkable response rates were not surprising and it certainly warrants longer trials.

Interestingly, a randomized, double-blind, placebo-controlled clinical trial of 30 breast cancer patients revealed that oral curcumin, 6.0 g daily during radiotherapy, reduced the severity of radiation dermatitis in breast cancer patients (Ryan et al., 2013). Curcumin in improved formulations have also proven to be safe and acceptable among patients in pilot studies (Irving et al., 2013; Kanai et al., 2013). Other ongoing clinical trials include Phase II combination therapy with standard radiation therapy and chemotherapy (capecitabine) in rectal cancer, Phase II trial to prevent colon cancer in smokers with aberrant crypt foci, Phase II trial in patients with pancreatic cancer, Phase II trial in patients with colorectal cancer, Phase I trial in patients with advanced cancer as well as Phase I trial to prevent colorectal cancer in patients undergoing colorectal endoscopy or colorectal surgery (Table 1).

Resveratrol is a polyphenolic compound present in grapes and red wine with potential anti-inflammatory and anticancer properties (Pervaz, 2003; Marques et al., 2009). It is used in traditional Chinese and Japanese medicine to treat dermatitis, gonorrhea, athlete’s foot and hyperlipemia (Aggarwal et al., 2004). In human LNCaP prostate carcinoma cells, resveratrol decreases PI3K/Akt signalling pathway and induces apoptosis (Aziz et al., 2006). Resveratrol is also shown to down-regulate the PI3K/Akt/mTOR signalling pathway, and combination with ramapycin further enhances the resveratrol-induced cell death in human U251 glioma cells (Jiang et al., 2009). In smooth muscle cells (SMC), resveratrol blocks the oxidized LDL (oxLDL)-induced activation of the mTOR pathway via PI3K/PDK1/Akt, thereby inhibiting oxLDL-induced SMC proliferation (Brito et al., 2009). In MDA-MB-231 and MCF-7 human breast cancer cells, resveratrol decreases mTOR and p70S6K phosphorylation, and in combination with rapamycin, suppresses the phosphorylation of Akt. An additive effect of resveratrol and ramapycin combination suggests some therapeutic value in breast cancer (He et al., 2010). In both estrogen receptor (ER)-positive and ER-negative breast cancer cells, resveratrol activates AMP-activated kinase (AMPK) and subsequently downregulates mTOR, 4E-BP1.
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**Table 1. The List Of Natural Compounds And Clinical Trial Phases**

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**mTOR Inhibitory Activities of Natural Phytochemicals**

Resveratrol has undergone numerous clinical investigations for its putative cancer chemopreventive properties. A pilot study of SRT501, a micronized resveratrol preparation, given as 5.0 g daily for 14 days, to patients with colorectal cancer and hepatic metastases scheduled to undergo hepatectomy, revealed a marked increase of cleaved caspase-3, a marker of apoptosis, in malignant hepatic tissue compared with tissue from the placebo-treated patients (Howells et al., 2011). In healthy volunteers, the ingestion of resveratrol caused a significant decrease in circulating IGF-1 and IGFBP-3 in all volunteers, suggesting chemopreventive activities (Brown et al., 2010).

In another study with healthy volunteers, daily intake of 1 g of resveratrol for 4 weeks revealed an induction of GST-pi level and UGT1A1 activity in individuals with low baseline enzyme level/activity, indicating that resveratrol can modulate enzyme systems involved in carcinogen activation and detoxification, suggesting a possible mechanism by which resveratrol inhibits carcinogenesis (Chow et al., 2010).

Unfortunately, a Phase II study of SRT501 (resveratrol) with bortezomib in patients with relapsed and/or refractory multiple myeloma has to be terminated recently (Popat et al., 2013). Out of 24 patients, 9 patients receiving SRT501 and bortezomib were withdrawn from the study, mainly due to serious adverse reactions. The predominant study finding was an unexpected renal toxicity and low efficacy of SRT501 with nausea and vomiting which could have...
resulted in disease progression and dehydration. This study has demonstrated an unacceptable safety profile and minimal efficacy in patients with relapsed/refractory multiple myeloma (Popat et al., 2013). At least two more clinical trials on colorectal cancer were completed but no published data was noted on the outcome. Currently an intervention study to examine the effects of resveratrol on neuroendocrine tumor is ongoing (Table 1).

Pomegranate, an ancient and mystical fruit of the tree Punica granatum L., has been used for centuries for the treatment of inflammatory diseases and disorders of the digestive tract (Faria and Calhau, 2010). In A/J mice, pomegranate fruit extract decreases carcinogen-induced lung tumorigenesis. Analysis of the murine lung tissue sample showed that pomegranate fruit extract down-regulates mTOR signalling by inhibiting the phosphorylation of PI3K, Akt and mTOR, and downstream molecules such as p70S6K and 4E-BP1 (Khan et al., 2007a). Other anti-carcinogenic effects of pomegranate fruit in numerous animal and cell culture models are well demonstrated in various studies (Kim et al., 2002b; Malik et al., 2005; Khan et al., 2007b).

In a Phase II clinical trial for men with rising PSA (prostate serum antigen) after surgery or radiotherapy for localized prostate cancer, patients were treated with 8 ounces of pomegranate juice daily (Pantuck et al., 2006). This study shows statistically significant prolongation on PSA doubling time over a period of 13 months. However, it was uncertain if improvements in biomarker like PSA doubling time are likely to serve as surrogate for clinical benefit. In a randomized Phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer, pomegranate extract treatment was associated with more than 6 months increase in PSA doubling time without adverse effects. Unfortunately, the significance of slowing of PSA doubling time remains unclear (Paller et al., 2013). Currently, clinical trials using either pomegranate juice or extract on prostate cancer patients are still ongoing (Table 1).

Genistein, the predominant isoflavone found in soybean (Glycine max (L.) Merr.), was found to have potent anti-tumor effects on prostate, brain, breast and colon cancers (Ravindranath et al., 2004; Hwang et al., 2009; Nakamura et al., 2009; Das et al., 2010; Sakamoto et al., 2010). In Hela and CaSkI cervical cancer cells, genistein inhibits cell growth by modulating various mitogen-activated protein kinases (MAPK) and inhibiting Akt phosphorylation (Kim et al., 2009). In MCF-7 breast cancer cells, genistein decreases protein expression of total Akt and phosphorylated Akt, suggesting that genistein could offer protection against breast cancer through down-regulation of the PI3K/Akt signalling pathway (Anastasius et al., 2009). Combination of genistein and indol-3-carbinol induces apoptosis and autophagy in HT-29 colon cancer cells by inhibiting Akt and mTOR phosphorylation (Nakamura et al., 2009). In addition, it inhibits Akt kinase activity and abrogates the EGF-induced activation of Akt in PC3 prostate cancer cells (Li and Sarkar, 2002). Genistein is also found to augment the efficacy of cisplatin in pancreatic cancer by down-regulating Akt expression (Banerjee et al., 2007).

The promising anti-cancer effects of genistein has led to Phase II clinical trials involving combination therapy of genistein with gemcitabine hydrochloride in stage IV breast cancer, genistein with gemcitabine and erlotinib in locally advanced or metastatic pancreatic cancer as well as genistein with vitamin D in men with early stage prostate cancer (Table 1). Other clinical trials of genistein include Phase II study in patients who are undergoing surgery for bladder cancer, Phase II study in patients with prostate cancer as well as Phase I study of genistein in preventing breast or endometrial cancer in healthy postmenopausal women (Table 1). A Phase II randomized, placebo-controlled trial was carried out to investigate whether daily, oral genistein (300 or 600 mg/d) as purified soy extract for 14 to 21 days before surgery alters molecular pathways in bladder epithelial tissue in 59 subjects diagnosed with urothelial bladder cancer (Messing et al., 2012). Overall, genistein treatment was well tolerated and the observed toxicities were primarily mild to moderate. A significant reduction in bladder cancer tissue p-EGFR staining was observed in low dose treatment group as compared with placebo. However, there were no significant differences in tumor tissue staining between treatment groups for COX-2, Ki-67, activated caspase-3, Akt, p-Akt and MAPK (Messing et al., 2012).

3,3′-diindolylmethane is a potential anticancer component found in cruciferous vegetables with anti-proliferative and antiangiogenic properties in human prostate cancer cells (Le et al., 2003; Garikapati et al., 2006). In DU145 human prostate cancer cells, the anti-proliferative effect of 3,3′-diindolylmethane was mediated by downregulation of PI3K, total Akt and phosphorylated Akt (Garikapati et al., 2006). BR-DIM, a formulated 3,3′-diindolylmethane with higher bioavailability, inhibits phosphorylation of Akt in C4-2B prostate cancer cells (Li et al., 2007b) and inhibits phosphorylation of Akt, mTOR, 4E-BP1 and p70S6K in platelet-derived growth factor-D overexpressing PC3 prostate cancer cells (Kong et al., 2008). A Phase I dose-escalation study of oral BR-DIM in castrate-resistant, non-metastatic prostate cancer patients revealed that BR-DIM was well tolerated and modest efficacy was demonstrated (Heath et al., 2010). In a pilot study to demonstrate the protective effect of BR-DIM supplements in postmenopausal women with a history of early-stage breast cancer, daily DIM (108 mg DIM/day) supplements for 30 days increased the 2-hydroxylation of estrogen urinary metabolites (Dalessandri et al., 2004). Currently, Phase II/III studies in patients with breast cancer and Phase II study in patients with stage I or stage II prostate cancer undergoing radical prostatectomy are ongoing (Table 1).

EGCG, a polyphenolic compound, is the major catechin found in green tea (Nagle et al., 2006). High consumption of green tea is associated with decreased risk of carcinogenesis and EGCG is a potent antioxidant that may have anticancer properties (Nagle et al., 2006; Katiyar et al., 2007; Pyrko et al., 2007). EGCG induces AMPK and p53 positive and negative human hepatoma cells, resulting in the suppression of mTOR and 4E-BP1, and a general decrease in mRNA translation (Huang et al., 2009).
In keloid fibroblast, EGCG inhibits the phosphorylation of Akt, p70S6K and 4E-BP1 (Zhang et al., 2006). Further studies are needed to establish the relationship between EGCG and PI3K/Akt/mTOR pathway and to determine whether mTOR mediates the effects of EGCG in treating brain, prostate, cervical and bladder cancers (Hsieh and Wu, 2009; Philips et al., 2009; Qiao et al., 2009; Das et al., 2010). However, many current clinical studies focus on using green tea extract or polyphenon E in a wide range of cancers such as breast cancer, leukemia, multiple myeloma and head and neck lesions (Table 1).

Timosaponin AIII is a steroidal saponin isolated from Anemarrhena asphodeloides Bunge (Liliaceae), a traditional Chinese medicine with anti-diabetic, anti-platelet aggregation and diuretic activities (Zhang et al., 1999). Timosaponin AIII has been reported to exhibit cytotoxicity towards HeLa cervical cancer cells and HCT-15 human colorectal cancer cells (Sy et al., 2008; Kang et al., 2011). Timosaponin AIII selectively induces cell death in BT474 and MDAMB-231 breast carcinoma cells, but not in normal MCF10A immortalized mammary epithelial cells. It exerts its anti-proliferative activity by inhibiting phosphorylation of Akt and mTOR, as well as p70S6K and 4E-BP1 (King et al., 2009). This compound is still in pre-clinical stages and has not progressed into clinical trials.

Gallic acid is a natural antioxidant polyhydroxyphenolic compound found in various plants and fruits (Chu et al., 2002; Sun et al., 2002). Gallic acid is also isolated from Phaleria macrocarpa (Scheff.) Boerl, an Indonesian medicinal plant which is used in traditional medicine to control cancer, impotence, hemorrhoids, diabetes mellitus, allergies, liver and heart disease. In preclinical studies, gallic acid induces apoptosis and inhibits cell growth of various cancer cell lines, including human TE-2 esophageal cancer, MKN-28 gastric cancer, HT-29 and Colo201 colon cancer, MCF-7 breast cancer, CaSki cervix cancer and mouse colon-26 colon cancer cells (Faried et al., 2007). It up-regulates the pro-apoptotic Bax protein, induces the caspase-cascade and down-regulates anti-apoptotic protein such as Bcl-2 (Faried et al., 2007). In human TE-2 esophageal cancer cells, gallic acid reduces the phosphorylation of Akt, mTOR and p70S6K, suggesting that the inhibitory effect of gallic acid was mediated by down-regulation of Akt/mTOR pathway (Faried et al., 2007).

Diosgenin is a naturally occurring plant steroid with potential antineoplastic activities as it induces apoptosis in various human cancer cell lines (Moalic et al., 2001; Liu et al., 2005). In human AU565 HER2-overexpressing breast adenocarcinoma cells, diosgenin down-regulates protein levels of fatty acid synthase (FAS), phosphorylated Akt and phosphorylated mTOR, suggesting that diosgenin may suppress FAS expression in AU565 cells through PI3K/Akt/mTOR signal transduction pathway (Chiang et al., 2007). High levels of FAS are associated with poor prognosis in human cancers, and it is highly elevated in HER2-overexpressing breast cancer cells (Kuhajda, 2000; Kumar-Sinha et al., 2003). In another study to determine effect of diosgenin on breast cancer cells, diosgenin is found to inhibit p-Akt expression and Akt kinase activity without affecting PI3 kinase levels. It causes G1 cell cycle arrest by down-regulating cyclin D1, cdk-2 and cdk-4 expression in breast tumor cells, resulting in inhibition of cell proliferation and induction of apoptosis. Interestingly, no significant toxicity was seen in the normal breast epithelial cells (MCF-10A). In vivo tumor studies indicate that diosgenin significantly inhibits tumor growth in both MCF-7 and MDA-231 xenografts in nude mice, indicating that it is a potential chemotherapeutic agent (Srinivasan et al., 2009). Diosgenin, timosaponin AIII and gallic acid are still in pre-clinical stages and have not progressed to clinical trials.

Conclusion

Hyperactivation of the PI3K/Akt/mTOR signalling pathway is a prominent hallmark of cancer and is frequently implicated in resistance to anticancer therapies such as biologics, tyrosine kinase inhibitors, radiation, and cytotoxics (Ballou and Lin, 2008). In therapeutic sensitivity restoration, inhibitors of the PI3K/Akt/mTOR pathway are often evaluated in combination with the other anticancer therapies in preclinical models and in clinical studies. Current preclinical and clinical evidences suggest that inhibitors of the PI3K/Akt/mTOR pathway in combination with other anticancer therapies are able to circumvent resistance by cancer cells. One of the important considerations of mTOR inhibitors would be the general tolerability and safety profile of the drugs. Although most of the reported toxicities are mild to moderate in severity and can be managed clinically by dose modification and supportive measures, efforts should continue to optimize leads with greater safety and better pharmacological profile. It is quite interesting that mTOR signalling pathway is not only implicated in various cancers but appears to be involved in multiple disease conditions. For example, rapamycin was also investigated for its longevity activity and lifespan extension possibilities. The relationship between age-associated diseases with mTOR and its signalling systems are intriguing. The mTOR signalling pathway clearly offers tremendous opportunities for discovery of new drugs that target both aging and its associated diseases (Sharp and Richardson, 2011).

Rapamycin and its analogues are versatile drugs with proven efficacy in cancer and new drugs produced promising results in various cancer-related clinical trials. Potential chemopreventive activities of some natural phytochemicals such as curcumin, green tea extract and pomegranate are convincing as more and more trials were carried out to provide evidence-based data to advocate chemoprevention of cancer. The challenge for the future will be to further dissect the molecular signalling pathway to fully understand the mechanisms underpinning sensitivity or resistance to mTOR inhibition. The uncover of these pathways and identification of novel drug targets will provide insight into rational combinations of mTOR inhibitors with classic cytotoxic agents, radiation, and other molecular targeted therapies in the treatment and prevention of cancer as well as to discover novel uses of this class of drugs.
References


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