



Preventive potential of *Andrographis paniculata*-derived compounds in metabolic syndrome-associated prostate cancer: A narrative review on the mechanism of action

Mohamad Khairul Hafiz Idris, Rosnani Hasham*

Department of Bioprocess and Polymer Engineering, School of Chemical and Energy Engineering, Faculty of Engineering, Universiti Teknologi Malaysia, Skudai, Malaysia.

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ABSTRACT

Metabolic syndrome (MetS) and prostate cancer (PCa) are among the diseases with a concerning prevalence. The reported cases for both medical dilemmas have been steady with no sign of abating at the moment. More worrying is that researchers have started to discover that some of the components of MetS associatively worsen the prognosis of PCa. Even though the relationship is not fully known, its manifestation could cause extra burden to the currently implemented treatment approaches. The use of plant bioactive compounds as an alternative treatment has gained recognition, provided that its mechanisms of action, tolerability, efficacy, safety, and cost-effectiveness are well understood. Therefore, the current review intended to highlight the potential of bioactive compounds derived from plants to simultaneously target MetS, PCa, and MetS-PCa codisease. Additionally, emphasis on the potential of *Andrographis paniculata* (AP) as a candidate for the treatment of MetS-PCa is also highlighted.

INTRODUCTION

The prevalence of prostate cancer (PCa) is increasing in our community. In Asian regions, the incidence of PCa has been on the rise from 5% in 1978 to 118% in 1997 in the indexed countries (Sim and Cheng, 2005), and there is no sign of this trend abating. At present, PCa is the sixth most frequent cancer among Asian men (Chen *et al.*, 2014). In other regions, similar trends have also been reported. PCa is among the top contributors that make up half of the overall burden of cancer in Europe in 2018 (Ferlay *et al.*, 2018). In a recent report published by the Ministry of Health of Malaysia, 3,132 cases were reported between 2007 and 2011. Following that, between 2012 and 2016, the total reported case increased to 4,189 (Azizah *et al.*, 2019). It is expected that by 2030, 1.7 million new PCa cases and 499,000 deaths will occur in

the entire world, and this cancer will be the most common in men in the future (Pakzad *et al.*, 2015).

The development of PCa is multifactorial. However, it has been observed that the progression is worse among individuals with metabolic syndrome (MetS), which comprises a series of systemic dysfunctions including high adiposity, hyperglycemia, hypertension, and dyslipidemia. A meta-analysis conducted on previously published academic manuscripts found that MetS was associated with a 12% increase in PCa risk. However, the association was only significant in the studies conducted in Europe but not in those in the USA and Asia. The same report also emphasized that hypertension and waist circumference of >102 cm were associated with a significantly higher risk of PCa at 15% and 56%, respectively (Esposito *et al.*, 2013). Nevertheless, another meta-analysis reported that men with MetS have a lower relative risk to develop PCa and its associated mortality. Yet, the same report highlighted that men with MetS are more likely to suffer from high-grade PCa and more advanced disease, and they are also at a greater risk of disease progression after radical prostatectomy and are more likely to succumb to PCa-specific death (Xiang *et al.*, 2013).

*Corresponding Author
Rosnani Hasham, Department of Bioprocess and Polymer Engineering,
School of Chemical and Energy Engineering, Faculty of Engineering,
Universiti Teknologi Malaysia, Skudai, Malaysia.
E-mail: r-rosnani@utm.my

One of the mediators between MetS and PCa is the high level of hormones and cytokines secreted by adipocytes. An earlier study reported that long-term exposure to high leptin levels significantly worsens PCa prognosis (Noda *et al.*, 2015). Additionally, the action of leptin is more pronounced in the androgen-resistant PCa cells (Hoda *et al.*, 2012). As such, the treatment approach using leptin antagonist has gained a great amount of research interest. For example, a leptin antagonist Leu-Asp-Phe-Ile (LDFI) has been successfully derived from amino acids and it was discovered to have growth and migration inhibitory effects on breast cancer cells after further testing in an animal model (Catalano *et al.*, 2015). Additionally, plant-derived leptin antagonist, honokiol, has been discovered from *Magnolia grandiflora*. It can negatively mediate the growth of breast cancer cells by inhibiting leptin-induced epithelial–mesenchymal transition (EMT) and mammosphere formation along with a reduction in the expression of stemness factors (Avtanski *et al.*, 2015). Apart from that, resveratrol has also been reported to reduce leptin expression from isolated rat adipocytes (Szkudelska *et al.*, 2009). This finding provides great insight into the potential of plant-derived bioactive compounds as one of the treatment strategies of PCa.

With these insights, the therapeutic potential of plant phytochemicals has been gaining more research attention. One such plant that has sparked great research interest is *Andrographis paniculata* (AP). AP is an herbaceous plant that is most commonly recognized as the King of Bitter, Kalmegh, or Hemptu Bumi (Mishra *et al.*, 2007). Traditionally, AP has been used to treat ailments such as fever, inflammation, viral and bacterial infections, and upper respiratory tract infection. It has also been used as an agent in the modulation of the immune system (Chao *et al.*, 2011; Saxena *et al.*, 2010). As a result, many discoveries have been made on the features of AP. Within the context of this review, AP has been found to inhibit the growth of cancer cells (Suriyo *et al.*, 2014) and some components of MetS (Islam, 2017). Therefore, AP is an herb with high potential for the treatment of PCa–MetS codisease.

METHODOLOGY

The literature for this review was conducted by searching various scientific electronic databases including Google Scholar, PubMed, Web of Science, SciFinder, Science Direct, American Chemical Society (ACS) Publications, Elsevier, and Wiley Online Library. Keywords used during the search were “AP” OR “Phytochemical” OR “Isolation” OR “PCa” OR “MetS” OR “Diabetes mellitus” OR “Hyperglycemia” OR “Hypertension” OR “Obesity” OR “Triglyceride” OR “Adipokine” OR “Cytokine”. Occasionally, these keywords were combined using the ‘AND’ search function to generate more specific and refined search results. Additional information was derived from other literature sources (books, journals, and thesis written in English). To provide the most current overview of the topic, the search was restricted to include sources published from 2000 onward. Only when extremely necessary to support the discussion of the review, earlier sources were included. The review emphasizes the pathological relationship between MetS components and PCa. Then, bioactive phytochemicals isolated from AP were studied as one of the promising agents to intervene in the disease relationship. Whenever possible, the mechanism of action of the bioactive compounds was also reviewed and discussed.

RESULT & DISCUSSION

Key component relationship between MetS and PCa

MetS is comprised of high adiposity, hypertension, dyslipidemia, and hyperglycemia that are suspected to play a significant role in the worsening of PCa prognosis (Figure 3). In men with dyslipidemia, a 9% increase in recurrence risk has been observed for every 10 mg/dl increase in cholesterol level (Allott *et al.*, 2014) and with elevated serum triglycerides, increased risk of recurrence after radical prostatectomy has also been noted. Moreover, Wright *et al.* (2013) reported that those with elevated glucose (≥ 100 mg/dl) had a 50% increased risk of recurrence compared to those with a normal glucose level (< 100 mg/dl). As a result, glucose levels at the time of PCa diagnosis are suggested to be an independent predictor of PCa recurrence. These findings suggest that there is some relationship between MetS with PCa development that warrants our attention. The following section discusses the key components linking MetS with PCa based on a thorough literature search.

Leptin

The core contributor of MetS is high adiposity. One of the physiological functions of adipocytes is the secretion of essential adipokines for regular systemic maintenance. For instance, leptin is required for the maintenance of energy homeostasis and in the balancing of body weight. Its deficiency or genetic defects in the components of the leptin signaling pathways can cause obesity (Zhou and Rui, 2013). However, in a pathological setting, leptin can pose deleterious effects in PCa development (Fig. 1).

An *in vitro* study revealed that long-term exposure to leptin can enhance the growth of all main PCa cell lines (LNCaP, DU145, and PC-3) (Noda *et al.*, 2015), where androgen-insensitive cells, DU145, and PC-3 show a stronger proliferative response (Hoda *et al.*, 2012). Leptin also induces the expression of vascular endothelial growth factor (VEGF), transforming growth factor- $\beta 1$ (TGF- $\beta 1$), and basic fibroblast growth factor in DU145 and PC-3 cells, stimulating cell survival, proliferation, and angiogenesis (Frankenberry *et al.*, 2004).

Leptin can influence estrogen metabolism and causes an increase in the expression of estrogen receptor (ER)- α and a decrease in ER- β (Habib *et al.*, 2015). At the same time, it can

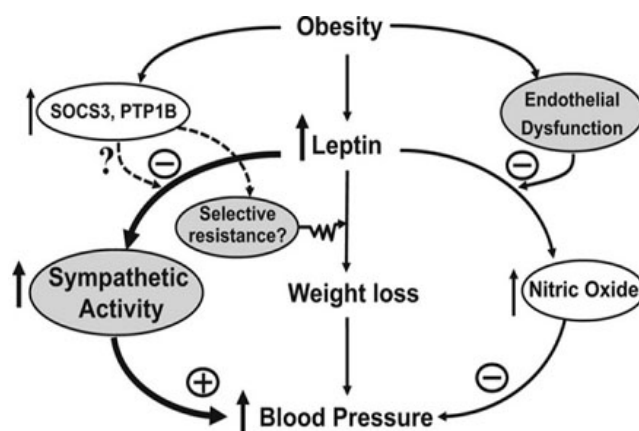


Figure 1. The role of leptin in the development of hypertension (Hall *et al.*, 2015).

also induce cellular migration of human PCa cells via upregulation of integrin and intracellular signal transduction (Huang *et al.*, 2011). Obese mice injected with murine androgen-insensitive PCa cell line RM-1 developed larger tumors and had stronger Ki-67 staining (Ribeiro *et al.*, 2010).

Tumor necrosis factor- α (TNF- α)

Adipocytes are also responsible for the secretion of TNF- α . They are needed to promote tumor apoptosis, enhance vascular permeability to allow passage of drugs to the tumor sites, and inhibit angiogenesis at a high concentration (Zidi *et al.*, 2010). TNF- α has also been reported to inhibit neovascularization, induce apoptosis of PCa cells, and stimulate antitumor immunity (Tse *et al.*, 2012).

Paradoxically, an experiment conducted on transgenic adenocarcinoma of the mouse prostate mice suggested that elevated TNF- α correlates with higher mortality (Xu *et al.*, 2015), suggesting TNF- α as one of the mediators to PCa. Its effect on other cancer cells, such as breast (Ma *et al.*, 2017) and colorectal (De Simone *et al.*, 2015), have also been reported. Simultaneously, there is evidence that it stimulates tumor angiogenesis, is involved in the initiation of PCa from an androgen-dependent to a castration-resistant state, and plays a role in EMT plasticity. Nevertheless, through meta-analysis, a recent study found that the dual effect of TNF- α on PCa is due to gene polymorphism (Ma *et al.*, 2014).

Interleukin-6 (IL-6)

IL-6 functions in the regulation of the immune system, the nervous system, liver regeneration, and the metabolic control of the body (Rose-John, 2012). However, in people suffering from obesity, the IL-6 level is higher than usual to the point that it becomes deleterious (Popko *et al.*, 2010). As it is one of the major inflammatory markers, its high concentration could gravely cause other problems. People with MetS are reported to have a higher inflammatory status, leading to other complications such as higher oxidative stress (Chen *et al.*, 2012a) and cancer (Braun *et al.*, 2011).

During PCa carcinogenesis, IL-6 and its receptors are elevated (Azevedo *et al.*, 2011). In patients with metastatic tumors, IL-6 acts as a chemoattractant. The expression of excessive IL-6 in the lung, liver, or brain may attract the circulating tumor cells (Knüpfner and Preiss, 2008). Moreover, IL-6 can shift from a paracrine growth inhibitor to an autocrine growth stimulator in PCa cells, supporting its role in castration-resistant prostate cancer (CRPC) development. At an elevated level, resistance toward chemotherapy is predictive (Bonuccelli *et al.*, 2014).

Elevated levels of IL-6 also stimulate hyperactivation of JAK/STAT3 signaling, which is often associated with poor treatment outcomes (Johnson *et al.*, 2018). IL-6 signaling can also activate ERK1/2 signaling, leading to resistance to chemotherapy and immune-evasive phenotype in several cancer cells, including PCa (Salaroglio *et al.*, 2019). The phosphoinositide 3-kinase (PI3K) signaling pathway is also activated by IL-6 in many cancers, causing cellular growth, survival, and proliferation. Overexpression of PI3K isoforms is also a cause for relapse and therapy resistance (Kim *et al.*, 2019). IL-6 also may be involved in the metastatic process of PCa through the regulation of EMT (Rojas *et al.*, 2011).

Micro-RNA 301a (miR-301a)

The elevated glucose level also has been known to increase the expression of miR-301a in PCa cells, thereby promoting G1/S cell cycle transition and accelerating cell proliferation (Li *et al.*, 2019). The overexpression of miR-301a may also activate the invasion/migration of PCa cells (Damodaran *et al.*, 2016). Also, high levels of miR-301a (above the median) were associated with an increased risk of biochemical recurrence (Nam *et al.*, 2016). Due to its differential expression in PCa and benign samples, it has been utilized as a marker for differentiating whether a sample is cancerous or not. Its expression has been reported to be significantly higher in both serum and tumor tissue in patients with PCa compared to patients with benign prostatic hyperplasia (BPH). Furthermore, the expression of miR-301a in prostatectomy specimens correlated with an increased Gleason score (Kolluru *et al.*, 2018).

EMT

Hyperglycemia could also modulate EMT by decreasing the E-cadherin level and increasing the N-cadherin level (Li *et al.*, 2016). Loss of E-cadherin facilitates dissociation of cancer cells from the tumor mass (origin site) and promotes tumor metastasis (Putzke *et al.*, 2011). Patients with hyperglycemia showed a decreased E-cadherin/N-cadherin (CDH1/CDH2) ratio in prostate tissue, an indication of EMT (Franko *et al.*, 2020).

Mature adipocyte cells also have been reported to secrete TGF- β 1 (El-Hattab *et al.*, 2020). In the hyperglycemic state, TGF- β 1 signaling hyperactivation is eventually causing a reduction in E-cadherin expression (Rahn *et al.*, 2018). This hormone has been described to affect the CDH1/CDH2 ratio through PI3K/AKT/mTOR and Smad signaling (Luo *et al.*, 2019).

Matrix metalloproteinases (MMPs)

At increased glucose concentrations, increased gene expression levels of MMPs have been detected (Franko *et al.*, 2020). Additionally, a high glucose (25 mM) level has been known to induce the activity of the collagenase (MMP-1) and gelatinase (MMP-2) (Death *et al.*, 2003). Elevated MMP activity promotes PCa progression not only by facilitating metastasis (Fig. 2) but also by profoundly impacting multiple steps of cell proliferation, apoptosis, angiogenesis, and EMT (Gong *et al.*, 2014). A report from Trudel *et al.* (2003) also indicated that both malignant and normal prostate cells express MMP-2, but higher levels of MMP-2 expression in malignant prostate glands were noted compared to its normal counterpart. Prostate tumor-derived MMP-3 has also contributed to metastatic tumor growth in the bone, both *in vitro* and *in vivo* (Frieling *et al.*, 2020).

Dyslipidemia

Dyslipidemia is also somewhat related to the pathogenesis of PCa. Low high-density lipoprotein cholesterol (HDL-C) level was found to be a risk and prognostic factor of PCa in several epidemiologic studies, although the overall linkage between HDL and PCa has not been definitively established (Kotani *et al.*, 2013). In a study conducted among Chinese people with PCa, the level of low-density lipoprotein cholesterol (LDL-C) and total cholesterol was significantly higher and the HDL-C level is much lower (Zhao *et al.*, 2017). Also, high triglyceride levels

were reported to correlate well with a higher incidence of PCa, especially in patients aged ≥ 60 years. This group also tends to present with a higher Gleason score of ≥ 8 (Hayashi *et al.*, 2012). A retrospective study on 843 radical prostatectomy patients revealed that elevated serum triglycerides were associated with an increased risk of PCa recurrence (Allott *et al.*, 2014). The mechanisms on how dyslipidemia correlates with PCa growth are still not yet elucidated. Some of the current meta-analyses concluded that the relationship is either not related (Cheng *et al.*, 2019) or

even inversely related (Ulmer *et al.*, 2009). Perhaps, the role of lipid only comes into play during stress situations. For example, under hypoxic conditions, significantly higher proliferation was observed in PCa cells following reoxygenation associated with rapid use of accumulated lipids (Schlaepfer *et al.*, 2015).

AP and its isolates as a potential agent to combat MetS-PCa codisease

AP is an herbaceous plant that is commonly known as Kalmegh (Bengali, Hindi), King of Bitter (English), Hempedu Bumi (Malay), Chuan Xin Lian (Chinese), Kirata (Sanskrit), and Shenshinren (Japanese) (Bone and Mills, 2013). It belongs to the family Achantaceae and it is ordinarily recognized based on its distinctive bitter taste. AP is known to be a native of India, Mainland China, and Taiwan. However, it can also be found in abundance in most Asian and south-east Asian countries (Hossain *et al.*, 2014). Despite its exclusive favor in the tropical and subtropical regions (owing to the moist nature), cultivation attempts in the temperate regions of the globe have also been reported. The geographical locality of AP is wide ranging. It can grow healthily on roadsides, hill slopes, moist lands, gardens, farms, plane lands, waste ground, forest, and seashores (Hossain *et al.*, 2014). Structurally, AP manifests the size of common shrubs with a height ranging from 30 to 110 cm.

The analysis of the crude alcohol extracts of the whole plant, leaf, and stem of AP revealed the presence of over 20 diterpenoids and over ten flavonoids. Among the most prominent phytochemicals, diterpenoid lactones stand out to be the most significant compound of AP, with andrographolide making up

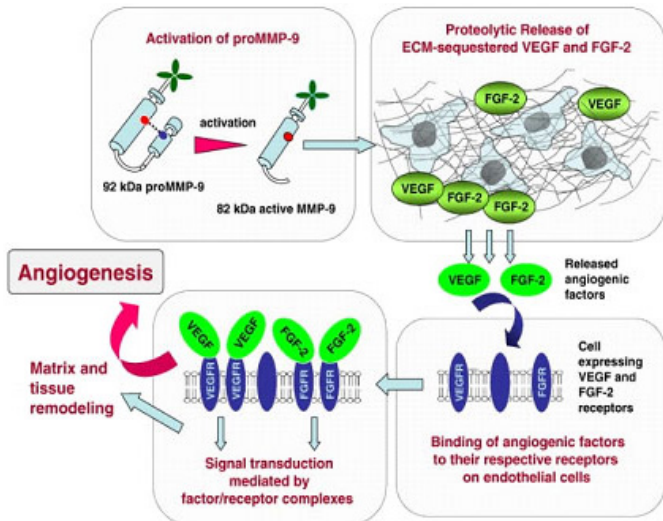


Figure 2. The action and relationship of VEGF and MMP-9 in the metastasis of cancer cells (Deryugina and Quigley, 2010).

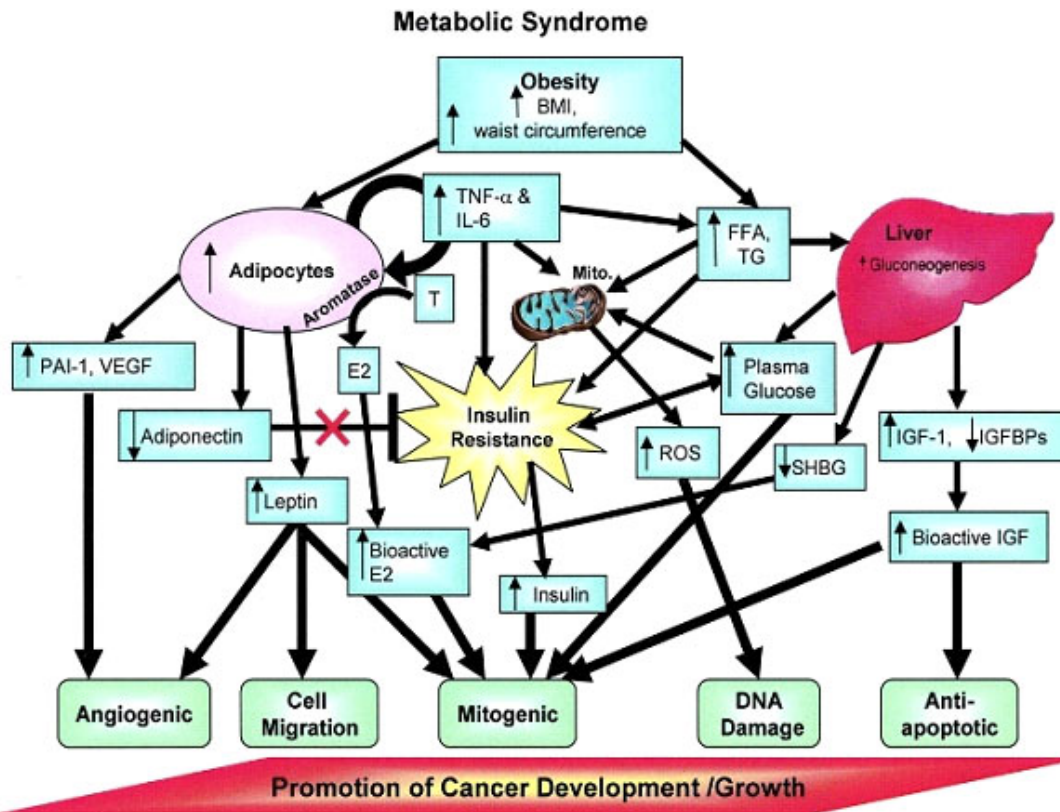


Figure 3. The relationship between MetS and cancer progression (Cowey and Hardy, 2006).

about 4%, 0.8%~1.2%, and 0.5%~6% in dried whole plant, stem, and leaf extracts, respectively (Chao and Lin, 2010). The other main diterpenoids are dehydroandrographolide, deoxyandrographolide, and neoandrographolide (Sriramaneni *et al.*, 2019) with contents amounting to 1.12%~1.97% (leaves) (Yanfang *et al.*, 2006), 0.57%, and 0.48%, respectively (Xu *et al.*, 2008).

These compounds are purported to reflect the therapeutic activities of AP owing to their significantly high amount. For this reason, several attempts have been undertaken by previous researchers to try to isolate and purify individual compounds for further exploration. For example, Chen *et al.* (2006) have reported successful isolations of 14 diterpenoids from AP using silica gel, Sephadex LH-20, ODS column chromatography, and high-performance liquid chromatography (HPLC). But the authors did not report any bioactivity of the isolated compounds. In another attempt, Wu *et al.* (2008) have successfully isolated 32 compounds including 14-deoxy-11,12-dihydroandrographolide, deoxyandrographolide, and neoandrographolide at high yield. After further testing, the author reported that 14-deoxy-11,12-dihydroandrographolide exerts potential as a vasorelaxation agent that is important in the management of hypertension. In all reports, the goal of isolation is to obtain a high purity compound. This is crucial because studies conducted on the high purity compound are more reflective toward the plant's bioactivities. This is also a critical part of the quality control of herbal medicines. Table 1 lists the studies that have attempted the isolation of phytochemicals from AP.

In the arena of cancer research, AP has become one of the most studied herbal candidates for the treatment of several cancer malignancies including PCa. However, for MetS, the application of AP as one of the potential treatment candidates is still scarce. Perhaps, the disease itself is still not yet fully understood, which hinders this undertaking. Nevertheless, it has been agreed that MetS can be definitively described by the presence of at least three of the following criteria: (1) abdominal adiposity, (2) hyperglycemia, (3) hypertension, (4) high triglyceride, and (5) low HDL-C (Huang, 2009). In view of this understanding, AP could be directed to target these components individually to fight MetS.

When considering both diseases as unlinked illnesses, the role of AP as a potential mediator could be conferred with some degree of certainty based on reported literature. AP, through

its isolated major diterpenoids, has been found to effectively inhibit the growth and progression of PCa cells. Geethangili *et al.* (2008) successfully isolated nine compounds from the aerial part of AP. When tested on a panel of cancer cell lines, almost all isolates exerted a prominent toxicity profile on Jurkat, PC-3, and Colon 205, except for HepG2. In another report, andrographolide was discovered to interfere with IL-6 signaling in both androgen-dependent and castration-resistant PCa cells, further inhibiting their progression (Chun *et al.*, 2010). In an animal model, andrographolide was implicated in the decrease of tumor volume, MMP-11 expression, and blood vessel formation at the tumor mass (Forestier-Román *et al.*, 2019).

In terms of MetS, AP has been reported to ameliorate hyperglycemia through inhibition of α -glucosidase activity by andrographolide and several of its derivative (Dai *et al.*, 2006), sensitization of the cell toward insulin by deoxyandrographolide (Arha *et al.*, 2015), and functional protection of insulin-producing cells by a modified compound, andrographolide-lipoic acid conjugate (Zhang *et al.*, 2009). Apart from that, andrographolide has been observed to effectively impede the obese manifestation by inhibiting lipid accumulation and improving serum lipid profile in high-fat diet-induced obese mice (Ding *et al.*, 2014). The hypertensive animal model has also been reported to present with normal blood status after administration with 14-deoxy-11,12-dihydroandrographolide (Yoopan *et al.*, 2007).

However, when taking both diseases as a connected illness, there has been no report on the role of AP as a potential therapeutic agent. But, by understanding the relationship between the two diseases, the putative therapeutic target of AP could be structured based on literary reports with a prudent consideration of the possible limitations. As such, Table 2 presents the list of potential targets of AP and some of its isolates in the management of MetS-PCa codisease based on the evidence laid out by previous researchers. But, based on literature studies, a lot of the reports were conducted using andrographolide as the focal point. Studies using isolates such as neoandrographolide, deoxyandrographolide, and dihydroandrographolide are reported much less frequently.

Enhancing bioavailability

The curative action of AP and its isolates can only be achieved when it can be successfully delivered to the targeted

Table 1. Several attempts by previous researchers in the isolation of phytochemical constituents from AP.

Source	Method	Isolated compound
(Harjotaruno <i>et al.</i> , 2007)	AP extraction using methanol > partitioned with ethyl acetate > silica column chromatography	Andrographolide
(Kulyal <i>et al.</i> , 2010)	AP extraction using 95% ethanol > fractioned into chloroform and methanol > methanol fraction was subjected to silica gel column chromatography with methanol (1.5%–21%) in chloroform > repeated column chromatography for purification	Andrographolide, 14-deoxy-11,12-didehydroandrographolide, 14-deoxyandrographolide, 3,14-dideoxyandrographolide, 14-deoxy-11-oxoandrographolide, 14-deoxy-12-hydroxyandrographolide, neoandrographolide, andrographiside, and 14-deoxyandrographiside
(Nugroho <i>et al.</i> , 2014)	AP extraction using 90% ethanol > fractionated at 1:10 (extraction-hexane)	Andrographolide-rich fraction
(Syukri <i>et al.</i> , 2016)	AP extraction using ethanol > partitioned with ethyl acetate > column chromatography using methanol : chloroform (1:9)	Andrographolide
(Sarkar <i>et al.</i> , 2019)	AP extraction using 95% methanol > silica gel (100–200 mesh) column chromatography > elution with petroleum ether-chloroform (1:1 and 1:4) and chloroform-methanol mixture with gradually increasing polarity > crystallization	14-Deoxy-11,12-didehydroandrographolide, andrographolide, and neoandrographolide
(Villedieu-Percheron <i>et al.</i> , 2019)	AP extraction using 100% methanol > flash chromatography over silica gel with elution gradient of methanol (3%–15%) in chloroform.	Andrographolide, dihydroandrographolide, and neoandrographiside

Table 2. Putative therapeutic target of AP in MetS–PCa codisease based on reported studies.

MetS–PCa pathology	Source	Compound	Mechanism of action	Limitation
TNF- α				
Highly expressed by the adipose tissue leading to enhanced proliferation of PCa.	(Qin <i>et al.</i> , 2006)	Andrographolide	Reduction TNF-a at mRNA level. Reduced production of TNF-a proteins in a concentration-dependent manner.	The experiment was conducted in murine peritoneal macrophages.
	(Thakur <i>et al.</i> , 2014)	Andrographolide	Both samples exert significant effect: blood TNF-α expressions in stressed rats were dose-dependently lowered by daily treatments.	Rats in the study did not bear prostate tumors.
	(Amaning Danquah <i>et al.</i> , 2020)	Andrographolide	In the cirrhotic lung, the TNF-α was highly expressed. Treatment with andrographolide significantly decreased the serum concentration of TNF-α.	Rats in the study did not bear prostate tumors.
	(Roy <i>et al.</i> , 2010)	14-Deoxyandrographolide	<i>In vitro</i> treatment of hepatocytes with this compound desensitizes the response of the cells toward TNF-α.	The study was conducted on a normal liver cell with the goal to inhibit cell death.
IL-6				
Autocrine and paracrine activity of IL-6 stimulate PCa cell growth.	(Chun <i>et al.</i> , 2010)	Andrographolide	The compound suppresses both IL-6 autocrine loop- and paracrine loop-induced cell signaling.	Mice studied did not present with the minimum criteria of MetS.
	(Zou <i>et al.</i> , 2016)	AP extract standardized at 1% mixture of andrographolide and dehydroandrographolide	Administration significantly reduces the excessive production of cytokines and chemokines including IL-6 in a dose-dependent manner.	Mice in the study did not present with minimum criteria MetS and prostate tumor.
	(Al Batran <i>et al.</i> , 2014)	Andrographolide	Treatment on rabbit at two different doses (10 and 20mg/kg) exhibited a significant reduction in IL-6 level.	Secretion of the IL-6 was not confirmed to originate from adipocytes, and the rabbit did not bear prostate tumor.
	(Liu <i>et al.</i> , 2008)	Andrograpanin	At 1.5 μM, andrograpanin significantly inhibited the expression of IL-6 from LPS-induced macrophage cells. Almost complete inhibition of IL-6 was noted at 90 μM.	Origin of IL-6 was not from adipocyte or PCa cell, and the animal did not bear prostate tumor.
Leptin				
Long-term exposure to elevated leptin from adipocyte can enhance the growth PCa cell lines (LNCaP, DU145, and PC-3). Leptin can activate cascades involved in cell survival particularly through the JAK2/STAT and PI3K/AKT pathways.	(Zhou <i>et al.</i> , 2010)	Andrographolide	Andrographolide was able to significantly suppress STAT3 phosphorylation and subsequent nuclear translocation. Achieved through suppression of JAK1/2 and interaction between STAT3 and gp130. STAT3 suppression by andrographolide enhances the sensitivity of the cancer cells to doxorubicin.	The study was not conducted on PCa cells.
	(Hsieh <i>et al.</i> , 2015)	Deoxyandrographolide	Deoxyandrographolide induces autophagy cell death by inhibiting the PI3K/AKT/mTOR pathway.	The study was not conducted on PCa cells.
	(Li <i>et al.</i> , 2015)	Andrographolide	Andrographolide inhibited hypoxia protein, HIF-1, in breast cancer cells by targeting the upstream PI3K/AKT pathway.	The study was not conducted on PCa cells.
miR-301a				
Hyperglycemia has been known to increase the expression of miR-301a in PCa cells, promoting cell cycle transition, proliferation, and invasion/migration of PCa cells by interfering with p21 and Smad4 expression (Li <i>et al.</i> , 2018).	(Yan <i>et al.</i> , 2012)	Andrographolide	Andrographolide treatment caused a dose-dependent increase in the expression of cell cycle inhibitors p21 and p27 in rheumatoid arthritis fibroblast-like synoviocytes (RAFLSs).	The study was not conducted on PCa cells.
	(Shi <i>et al.</i> , 2008)	Andrographolide	Cell cycle arrest at the G1/S phase was observed in Lovo cells after treatment with andrographolide at concentrations of 0–30 μM. The expression of CDK inhibitor, p21, was significantly increased.	The study was not conducted on PCa cells.
	(Li <i>et al.</i> , 2020)	Andrographolide	Treatment of human alveolar epithelial cells (AECs) with andrographolide interfered with Smad4 nuclear translocation, repressing gene expression required for cell growth.	The study was not conducted on cancer cells.
EMT				
Hyperglycemia could modulate EMT in prostate tumors.	(Li <i>et al.</i> , 2020)	Andrographolide	Andro inhibited TGF-β1-induced EMT and EMT-related transcription factors in alveolar epithelial A549 cells.	The test was not conducted on PCa cells.
	(Liu <i>et al.</i> , 2019)	Deoxyandrographolide	Deoxyandrographolide treatment effectively rescued the EMT of osteosarcoma cells.	The test was not conducted on PCa cells.
	(Kayastha <i>et al.</i> , 2015)	Andrographolide	EMT markers, α-SMA, fibronectin, and collagen IV, were significantly decreased after treatment with andrographolide in lens epithelial cells (LECs). Andrographolide inhibits avert EMT by inhibiting the mitogen-activated protein kinase (MAPK) signaling pathway.	The study was not conducted on cancer cells.

(Continued)

MetS-PCa pathology	Source	Compound	Mechanism of action	Limitation
E-cadherin				
In hyperglycemic condition, the level of E-cadherin in PCa cells is reduced. This leads to EMT of the cancer cells that eventually promote metastasis and invasion.	(Hsieh <i>et al.</i> , 2017)	Dehydroandrographolide	Dehydroandrographolide significantly induced the expression of E-cadherin in human oral cancer cell lines (SCC9). EMT-related proteins, including Vimentin, Zo-1, Zeb-1, Twist-1, Snail, Slug, N-cadherin, and β -cadherin, were decreased.	The test was not conducted on PCa cells and element of MetS was not incorporated.
	(Xia <i>et al.</i> , 2019)	Andrographolide	In the lung tissue of the mouse model, exposure to cigarette smoke extract (CSE) decreased the level of E-cadherin. Andrographolide blocked the decreases of E-cadherin levels induced by CSE.	The animal model did not confer MetS and the target was not done in tumor cells.
	(Liu <i>et al.</i> , 2017)	Andrographolide	Andrographolide sustained the expression of E-cadherin in human osteosarcoma (bone cancer) cell, U-2 OS. The treatment inhibits EMT, metastasis, and invasion of the cancer cell.	MetS microenvironment was not introduced and the study was not done on PCa cells.
TGF-β1				
Hyperglycemia activates the TGF- β 1 signaling that eventually causes a reduction in E-cadherin.	(Lin <i>et al.</i> , 2018)	Andrographolide	Andrographolide ameliorated both liver inflammation and fibrosis through inhibiting the activation of the TLR4/NF- κ B and TGF- β 1/Smad2 signaling pathways in hepatic stellate cells (HSC).	The study was not conducted in MetS setting, and test on PCa cells was not included.
	(Lee <i>et al.</i> , 2010)	Andrographolide and 14-deoxy-11,12-didehydroandrographolide	With high glucose treatment (25 mM), the secreted TGF- β level was upregulated to 2.5 times in murine kidney cell line, MES 13. Andrographolide and 14-deoxy-11,12-didehydroandrographolide showed significant effects in reducing TGF- β levels secreted. 14-Deoxy-11,12-didehydroandrographolide is more potent.	The study was not conducted on cancer cells.
MMPs				
At increased glucose concentration, increased gene expression levels of MMPs have been detected which promotes PCa progression and metastasis.	(Zhang <i>et al.</i> , 2017)	Andrographolide	Antiproliferation effects of andrographolide on the human colorectal adenocarcinoma, SW620, cells were associated with the inhibition of MMP-9 signaling activation.	Study did not incorporate MetS condition and without PCa cells.
	(Shi <i>et al.</i> , 2009)	Andrographolide	Andrographolide inhibited dose-dependently the migration and invasion of metastatic human colorectal adenocarcinoma, Lovo cells. The treatment diminished the activity and the mRNA and protein levels of MMP-7.	Study did not incorporate MetS condition and without PCa cells.
	(Chao <i>et al.</i> , 2013)	Andrographolide	Andrographolide dose-dependently inhibited TPA-induced MMP-9 protein expression, enzyme activity, migration, and invasion in MCF-7 breast cancer cells.	Study did not incorporate MetS condition and without PCa cells.

site. But its low bioavailability has been a major challenge in drug delivery research. The bioavailability of AP was described to be only 2.67% and structural modification quickly takes place in duodenum and jejunum. Specifically, for andrographolide, low bioavailability is caused by high lipophilicity, low water solubility, and efflux by P-glycoprotein (Pandey and Rao, 2018). A low circulating concentration puts a limit on the therapeutic actions of the drug at the disease location.

One of the strategies that have been utilized is by incorporating the absorption enhancer. Andrographolide integrated into polymer solid dispersion (SD) formulation was reported to elevate its C_{max} /dose and the area under the curve (AUC)/dose by 3.7-fold and 3.0-fold, respectively (Yen *et al.*, 2020). An SD utilizing silica, SiO₂, was also fabricated by another researcher. *In vitro* testing revealed that the SD enhances the drug by improving its solubility and drug release profile (Zhang *et al.*, 2016).

The strategy of using nanoparticle has also been employed. There are several nanoparticle formulations that have been developed with fitting criteria to be used as a stable drug carrier such as liposome, solid-lipid nanoparticles (SLN), and nanostructured lipid carrier. Andrographolide-loaded herbosome

incorporating soya-phosphatidylcholine has been formulated by Jain *et al.* (2013) in an effort to deliver its hepatoprotective properties. The authors reported better liver function and drug absorption in the rat model using the nanoparticle as compared to administration with free andrographolide. Graverini *et al.* (2018) have also attempted to deliver andrographolide to the brain as a strategy to treat neurodegenerative complications. However, the blood-brain barrier posed limited passage of the compound. By using SLN as the carrier, the compound was able to overcome the barrier. Semipurified andrographolide formulated into nano-phyto vesicle was also able to increase its bioavailability (Verma *et al.*, 2020). To further enhance cellular uptake, the nanoparticles could also be improved by integrating the structure with cell-penetrating peptide (Chen *et al.*, 2012b).

CONCLUSION

In conclusion, the link between MetS and PCa is mediated by a number of mechanisms including leptin, TNF- α , IL-6, miR-301a, EMT, and MMPs. AP and its isolates have great potential to intervene in these linkages. Previous studies have presented proof of concept on the capacity of AP and some of its isolates in

targeting mechanisms involved in the MetS–PCa relationship. In particular, andrographolide has been reported repeatedly to have inhibitory capability in all relationships discussed. This review is hoped to open a new window of opportunity for AP as one of the treatment approaches for MetS–PCa codisease.

AUTHOR CONTRIBUTIONS

Conceptualization: Idris, M. K. H. Data curation: Idris, M. K. H. Supervision: Hasham, R. Writing – original draft: Idris, M. K. H. Writing – review and editing: Hasham, R.

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CONFLICT OF INTEREST

The author declares that there are no conflicts of interests.

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