

# Metabolic disorders and cancer: is there a role for nutraceuticals?

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ABSTRACT

Obesity and overweight are defined as abnormal excess accumulation of fat in adipose tissue, which is recognized as a real organ with both metabolic and endocrine functions, and have a close relationship with oncological risk. The relationship between obesity and carcinogenesis is complex and not fully understood. However, obesity is frequently associated with several pathological states such as chronic inflammation, dyslipidaemia and insulin resistance (generally defined as metabolic disorders) which contribute to the increased risk of cancer in the overweight population. Current data show that metabolic disorders are often reversible with prompt therapeutic intervention, so these conditions and related carcinogenetic pathways should be managed for cancer prevention and therapy. Metformin and statins have demonstrated their ability to interfere with tumour processes but unfortunately also produce side effects, making long-term and preventative use difficult. Some nutraceutical compounds seem to be ideal for providing similar activity and effectiveness as these agents but with minor or absent side effects. This review examines the pathophysiology of metabolic disorders, their relationship with cancer and the possibility of interfering with associated processes with some promising nutraceuticals used as monotherapy or in combination with conventional therapies.

## Keywords

Obesity  
Cancer risk  
Insulin resistance  
Nutraceuticals

## Introduction

Obesity and overweight have become major public health concerns during the last few decades as they are key risk factors for type 2 diabetes, cardiovascular disease, dyslipidaemia, hypertension and some cancers [1].

The precise mechanisms that underlie the association between obesity and some cancers, and the accompanying metabolic changes in the surrounding microenvironment, remain unclear, but it is generally accepted that excess fat and adipose tissue hypertrophy disrupt the dynamic role of the adipocyte in energy homeostasis, resulting in inflammation and alteration of adipokine (for example, leptin and adiponectin) signalling [2]. Additionally, secondary changes related to insulin signalling, such as the presence of insulin resistance (IR) and hyperinsulinaemia, in addition to lipid dyslipidaemia (hypercholesterolaemia), may also promote

cancer development [3]. Therefore, the association between obesity and cancer risk should be considered in terms of metabolic disorders where each condition contributes to cancer risk and is a potential target of conventional and/or nutraceutical therapy.

## Obesity, overweight and cancer risk

Cancer is predicted to overtake heart disease as the leading cause of death worldwide. The global obesity/overweight epidemic has been increasing over the past 30 years, resulting in more than 600 million obese/overweight adults [4]. Cancer is generally considered a genetic disease, with the first step in carcinogenesis caused by genetic damage to the genome. Importantly, this damage is either inherited or acquired during life as a result of an unhealthy lifestyle [5]. Essentially, one-third of the risk for cancer is attributed to dietary and lifestyle factors, particularly those which cause metabolic disorders.

Growing evidence from epidemiological, preclinical and clinical studies indicates that increased adiposity is associated with increases in cancer incidence and mortality [6]. Renehan *et al* [7] published a meta-analysis and systematic

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review assessing the strength of association between body mass index (BMI) and different sites of cancer. The authors found that increased BMI is associated with an increased risk of common and less common malignancies. In particular, a 5 kg/m<sup>2</sup> increase in BMI in men was strongly associated with oesophageal adenocarcinoma and with thyroid, colon and renal cancers, while in women the greatest increase in relative risk (RR) was observed for endometrial, gallbladder, oesophageal and postmenopausal breast cancer. The association between BMI and cancer mortality has been extensively analyzed. A prospective study of more than 900,000 adults with over 57,000 deaths from cancer found an association between BMI and cancer mortality and reported also that individuals with a BMI of at least 40 had increased cancer mortality (RR 1.52 for men and 1.62 for women) [8]. A higher mortality risk in obese subjects was reported for most cancers for both sexes with the highest RR found for liver cancer in men and for uterine, pancreatic and breast cancer in women. Overall, 14% of all cancer deaths in men and 20% of all cancer deaths in women are attributable to overweight and obesity. Epidemiological data on incidence and BMI-related mortality are summarized in Fig. 1.

Recently, the population-attributable fraction (PAF; the proportion of cancers potentially avoidable if the obesity–cancer association is causal) for obesity and cancer risk worldwide has been calculated [9]. Approximately 3.6% of all new cancers may be due to high BMI. Interestingly, the PAF in women is more than double that in men, reflecting the strong relationship between obesity and hormonal neoplasia, for instance of the uterus and breast. Had BMI remained at the levels seen before the obesity epidemic, in particular in better developed countries, approximately 25% of cancers related to high BMI in 2012 could have been avoided. An increased cancer risk is also seen in some metabolic conditions frequently found in the general population, such as metabolic syndrome. Metabolic syndrome is a cluster of risk factors for cardiovascular disease and type 2 diabetes and is a growing problem worldwide [10]. The factors include obesity (particularly central adiposity), glycaemic perturbations, raised blood pressure, elevated triglyceride levels and low high-density lipoprotein (HDL) cholesterol levels. A recent systematic review and meta-analysis [11] on almost 40,000 cancer cases supports the emerging hypothesis that metabolic syndrome may be associated with risk for some common cancers. Interestingly, the same tumour-related cancers as seen in obesity are also seen in metabolic conditions in both men and women.

### The links between metabolic disorders and cancer

The relationship between obesity and carcinogenesis is complex and not fully understood. Obesity is defined as abnormal excess accumulation of fat in adipose tissue, which is recognized as a real organ with both metabolic and endocrine functions [12]. Body fat increases in volume due to excessive accumulation of triglyceride inside white adipocytes. This cell hypertrophy results in hypoxia and necrosis, and although the sequence of events remains unclear, the related conditions of IR, chronic inflammation with cytokine production and reversal of the leptin-to-adiponectin (L–A) ratio, and altered production and regulation of the lipid profile and steroid hormones are considered to contribute to the increased cancer risk in this population.

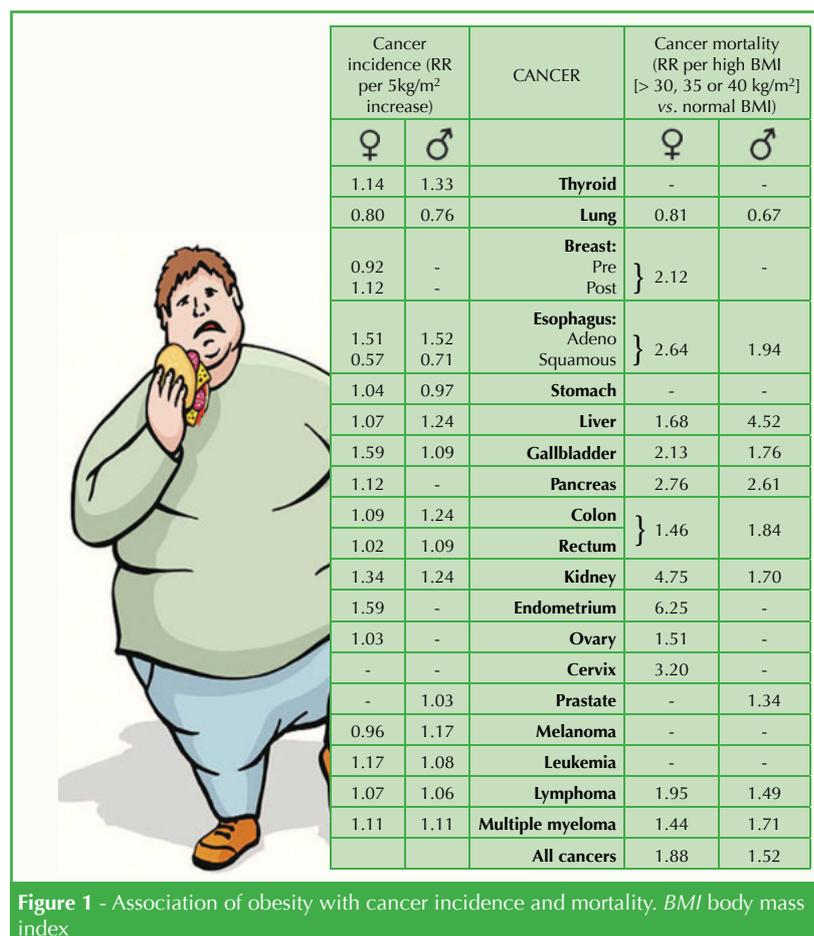


Figure 1 - Association of obesity with cancer incidence and mortality. BMI body mass index

### Subclinical chronic inflammation

The precise physiological events leading to the initiation of the inflammatory response in obesity remain incompletely understood. It is possible that hypoxia associated with adipocyte hypertrophy stimulates cellular stress pathways resulting in the onset of cell-autonomous inflammation and the release of cytokines and other pro-inflammatory signals. In particular, there is an increase in pro-inflammatory cytokines such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-6, IL-1 and plasminogen activator inhibitor-1 (PAI-1) that constitute a sort of 'inflammation group' which promotes oncogenic effects [13]. The presence of these cytokines causes activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B), a transcription factor which is inactive under physiological conditions but can be activated by carcinogens. NF- $\kappa$ B has been shown to influence several oncogenic pathways, suppressing apoptosis and inducing cellular transformation, proliferation, invasion, metastasis, chemoresistance, radioresistance and/or inflammation [14]. Another feature of the obesity inflammatory response is increased infiltration of immune cells (including T cells, macrophages and dendritic cells) into metabolic tissues. It has been shown that infiltration of macrophages and other immune cells into adipose tissue contributes to the emergence and maintenance of obesity-induced inflammatory responses, including their carcinogenetic properties [15].

Chronic inflammation also influences the production of and relationship between leptin and adiponectin, two proteins secreted by adipocytes. Leptin levels increase in obesity and decrease during fasting [16], while adiponectin levels are reduced in both obesity and fasting. Biological studies have shown that adiponectin is inversely associated with obesity and hyperinsulinaemia [17] and also appears to have anti-inflammatory, anti-angiogenic, pro-apoptotic and antidiabetic properties [18]. It decreases the expression of vascular endothelial growth factor (VEGF) while increasing the activity of p53 and the caspase pathway (pro-apoptotic). In contrast, leptin is involved in cell proliferation, angiogenesis and metastasis, increasing the expression of anti-apoptotic proteins, inflammatory markers (TNF- $\alpha$ , IL-6), angiogenic factors (VEGF) and hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) [19]. Moreover, recent evidence demonstrates that the L-A ratio could be a useful index and surrogate marker for IR and its associated cancer risk. In accordance with these biological activities, an increased L-A ratio and, conversely, a reduced A-L ratio have been associated with risk for several types of cancer including endometrial, breast, prostate and colon cancer.

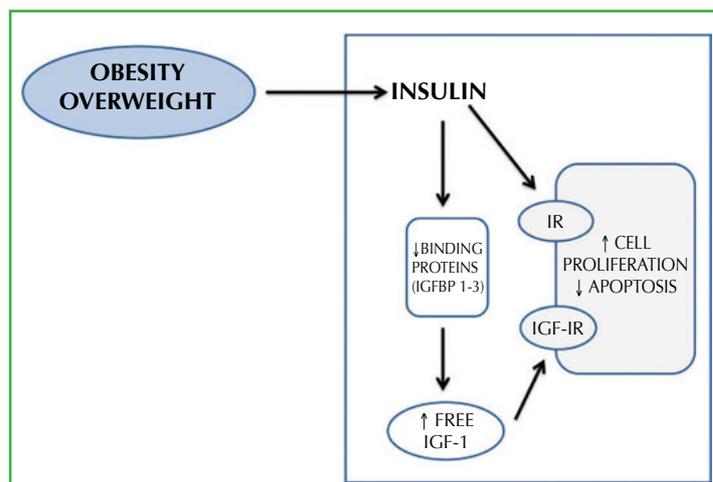
### Insulin resistance

Associated with chronic subclinical inflammation, excess visceral adiposity also causes IR – a pathological condition characterized by a decrease in the efficiency of insulin signalling for blood sugar regulation – and dysmetabolism, which are collectively known as metabolic syndrome.

Metabolic syndrome is strongly associated with IR and may therefore be a potential surrogate marker of this metabolic disorder. Prospective cohort studies have shown that metabolic syndrome is closely associated with the increased incidence of and/or mortality from a broad range of site-specific malignancies [11], suggesting the central role of IR in linking obesity and cancer.

Insulin is secreted by the  $\beta$ -cells of the pancreas in response primarily to glucose and fatty acid levels. Obesity-induced IR (and consequently hyperglycaemia) is compensated for by an increase in insulin secretion, leading to fasting and postprandial hyperinsulinaemia. Both insulin and glucose are elevated in obesity-related IR and have been implicated in cancer risk and prognosis [20].

The mechanism linking metabolic syndrome and IR to cancer is complex and not fully understood, but we propose a simple hypothesis which involves the insulin-IGF axis, related to cellular metabolic reprogramming which always occurs in cancer cells [21]. Our hypothesis postulates that excess body weight is associated with a prolonged hyperinsulinaemic state which consequently reduces the production of some IGF-binding proteins, in particular IGFBP-1 and IGFBP-2, with resultant increases in the levels of free and 'bio-active' IGF-I [22] (Fig. 2).



**Figure 2** - Hypothesis which links insulin resistance to cancer. Excess body weight is associated with prolonged hyperinsulinaemia which reduces the production of some IGF binding proteins, in particular IGFBP-1 and IGFBP-2, with resultant increases in the levels of free and bio-active IGF-I. Both insulin and IGF stimulate their cellular receptors (IR and IGF-1R) activating their mitogenic and carcinogenetic effects

Both insulin and IGF stimulate their cellular receptors (IR and IGF-R), activating their mitogenic and carcinogenic effects. Various metabolic pathways have also been implicated in the multistep development of tumours, and a metabolic shift from catabolic to anabolic metabolism is a classic hallmark of cancer cells. This metabolic reprogramming, known as the Warburg effect [23], results in the use of aerobic glycolysis in preference to oxidative phosphorylation (OXPHOS) for increased energy production in cancer cells (Fig. 3). This condition is closely related to glucose availability (cancer cells consume an excessive quantity of glucose) and so the presence of hyperglycaemia related to metabolic syndrome/IR ensures an ideal microenvironment for cancer cell proliferation and growth.

### Sex hormones and hypercholesterolaemia

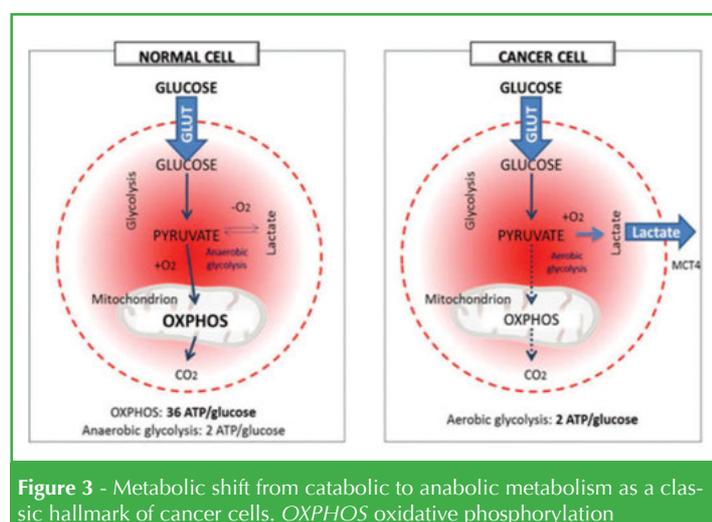
The synthesis and bioavailability of sex hormones (oestrogens, androgens and progestins) are influenced by obesity and overweight. These hormones are directly associated with cancer risk and outcome, in particular with tumour development in hormonal-sensitive tissue [12]. Several pathways are implicated in this relationship, but activation of the enzyme aromatase and insulin levels seem to be the key pathways involved. Adipose tissue promotes the expression of aromatase which converts androgens to oestrogens, while maintaining their regulation of cellular differentiation, proliferation and apoptosis [24]. Moreover, the presence of hyperinsulinaemia in these patients reduces hepatic synthesis and consequently the concentrations in the blood of sex-hormone-binding globulin (SHBG) which in turn increases the bioavailability of free oestrogens. A pooled analysis of nine prospective cohort studies [25] demonstrated that the risk of breast cancer increases in postmenopausal women with higher concentrations of circulating sex steroids. More-

over, another analysis showed that the association between increased BMI and the risk of postmenopausal breast cancer is almost entirely due to the concomitant increasing concentration of either total or bio-available oestradiol in the blood [26]. Finally, cholesterol is a fundamental precursor of steroid hormones that have long been recognized as regulators of both cell proliferation and differentiation, intimately associated with some types of cancer with a hormonal aetiology [27]. In addition, an intermediate of cholesterol metabolism, 27-hydroxycholesterol (27-HC), which is synthesized by the enzyme cholesterol 27-hydroxylase (CYP27A1), is able to bind to the oestrogen alpha receptor on epithelial cells of the mammary gland, activating the related pathways [28]. Last but not least, cholesterol seems to influence apoptosis and the invasiveness of cancer cells due its crucial action on the cell membrane with the organization of lipid rafts, and also its ability to stimulate local aromatase expression [29]. Consequently, hypercholesterolaemia which usually accompanies obesity, provides cells with a suitable substrate for proliferation (hormones and activated oestrogen receptor) with a consequent increased risk of carcinogenesis.

### Therapeutic interventions

Clinicians use various agents to target the principal pathways involved in these relationships to prevent and treat cancer in patients with metabolic disorders. The inflammatory state, IR and hypercholesterolaemia are pathways targeted by drugs such as NSAIDs, metformin and statins to prevent and treat cancer.

Metformin is a biguanide derivative, currently approved for the treatment of non-insulin dependent diabetes mellitus, and an insulin-sensitizing agent with potent antihyperglycaemic properties. Observational studies have shown that metformin treatment is associated with reduced cancer risk. In particular, Evans *et al* [30] demonstrated that patients with diabetes treated with metformin had a lower incidence of any cancer compared with patients on other treatments. Another observational study [31] involving more than 10,000 patients with diabetes treated with metformin or other antidiabetic agents showed a lower cancer-related mortality rate in the metformin group compared with groups receiving other drugs such as sulfonylureas or insulin. These promising data were confirmed in a recent meta-analysis [32]. Several preclinical and clinical studies in the last few decades have confirmed the effect of metformin on the incidence and prognosis



**Figure 3** - Metabolic shift from catabolic to anabolic metabolism as a classic hallmark of cancer cells. OXPHOS oxidative phosphorylation

of many types of cancer. The studies suggest that metformin may have different mechanisms of tumour inhibition via insulin-dependent and independent pathways [33], including activation of adenosine monophosphate kinase (AMPK) with inhibition of cancer proliferation and apoptosis induction in cancer cell lines [34]. A recent presurgical trial evaluated changes in Ki-67 between pretreatment biopsy and post-treatment surgical specimens and indicated Ki-67 has prognostic value and may predict antitumor activity in breast cancer. The research showed that metformin administered before surgery did not significantly reduce Ki-67 overall but had a significantly opposite effect depending on IR, particularly on luminal B tumours [35]. There was a mean proportional decrease in Ki-67 of 10.5% in women with a HOMA score  $>2.8$ , while an opposite increase of 11.1% was observed in women with a HOMA score  $<2.8$ . Interestingly, similar drug effects on Ki-67 were noted depending on BMI, waist/hip ratio, alcohol consumption and C-reactive protein (CRP). Moreover, an overall reduction in CRP and total cholesterol was noted in the metformin group. These findings confirm that metabolic disorders directly influence cancer risk and outcome, and so these disorders should be treated to combat cancer.

Statins (HMG-CoA reductase inhibitors) are the most popular cholesterol-lowering drugs because of their efficacy and economic profile. Randomized controlled trials (RCTs) have shown that statins improve the blood lipid profile, decrease the incidence of cardiovascular disease and reduce mortality from coronary heart disease [36, 37]. Moreover, in the last few decades, the recognized relationship between metabolic disorders (including hypercholesterolaemia) and cancer promotion and progression, has led to growing interest in statins because of their possible use as anticancer agents. Statins have been associated with a significantly lower risk of breast, colorectal, ovarian, pancreatic and lung cancer and lymphoma in several observational studies [38], but generally results concerning cancer risk and incidence remain controversial. This may be due to the heterogeneity of many factors such as statin type, dose, exposure times and individual patient characteristics. However, while the effects of statins on cancer prevention remain inconclusive, their impact on cancer mortality and progression is clear. A recent systematic review and meta-analysis of 95 cohort studies including more than 1 million patients [39] showed that statin use was significantly associated with a decreased risk of all-cause mortality (HR 0.70, 95% CI 0.66 to 0.74) compared with no use. The analysis also showed a significant reduction in cancer-specific mortality (HR 0.60, 95% CI 0.47 to 0.77),

with a concomitant increase in progression-free survival (HR 0.67, 95% CI 0.56 to 0.81), recurrence-free survival (HR 0.74, 95% CI 0.65 to 0.83) and disease-free survival (HR 0.53, 95% CI 0.40 to 0.72). These data indicate that statins are likely to serve as adjuvant treatment for cancer patients, especially those needing lipid-lowering treatment.

Moreover, recent findings confirm that the relationship between hypercholesterolaemia and cancer (in particular hormonal cancer) is largely supported by cholesterol's function as a precursor of steroid hormones and metabolic intermediates such as 27-HC. Consequently, cholesterol-lowering medication (statins in particular) during adjuvant endocrine therapy may have a role in preventing breast cancer recurrence in hormone receptor-positive early-stage breast cancer. The Breast International Group (BIG) conducted a randomized, phase III, double-blind trial (BIG 1-98) of over 8000 postmenopausal women with early-stage, hormone receptor-positive invasive breast cancer [40]. The aim of the study was to compare the efficacy of aromatase inhibitors and tamoxifen, and the primary endpoint was disease-free survival. The results showed that breast cancer outcome was better with letrozole than with tamoxifen. Tamoxifen's ability to reduce serum cholesterol was confirmed but with letrozole administration, serum cholesterol remained at pretreatment levels suggesting (for the first time in a clinical setting) a beneficial effect of cholesterol-lowering medication (CLM) on breast cancer outcome [41]. These data demonstrate that the use of CLM in women with early-stage, hormone receptor-positive invasive breast cancer, reduces recurrence, indicating that high serum cholesterol levels make adjuvant hormonal therapy less effective.

## What role for nutraceuticals?

Drugs to control metabolic disorders, and consequently reduce cancer risk and improve outcome, often have side effects which result in reduced compliance. Both metformin and statins have fairly serious side effects (summarized in Fig. 4) which hinders their use in preventive therapy or in combination with long-term cancer therapy with its own side effects or complications. Therefore, we need to find alternative/synergistic compounds with similar activity and effectiveness but with fewer or no side effects. The most cost-effective approach is still to modify diet and physical activity, but lifestyle programs are often difficult to follow and may not significantly reduce risk. However, some nutraceuticals have been studied for their ability to modify the cancer risk parameters associated with metabolic disorders.

Metformin side effects	Statin side effects
<p><b>Very common</b> (affecting over 1 in 10 people taking metformin):</p> <ul style="list-style-type: none"> <li>• Disturbance to the gut</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Diarrhoea</li> <li>• Abdominal pain</li> <li>• Loss of appetite.</li> </ul> <p><b>Common</b> (affecting between 1 in 10 and 1 in 100 people taking metformin):</p> <ul style="list-style-type: none"> <li>• Taste disturbance, usually a metallic taste.</li> </ul> <p><b>Very rare</b> (affecting less than 1 in 10,000 people taking metformin)</p> <ul style="list-style-type: none"> <li>• Elevated levels of lactic acid in the blood (lactic acidosis)</li> <li>• Decreased absorption of vitamin B12 during long-term use</li> <li>• Skin reactions such as rash, itching or flushing</li> </ul>	<p><b>Common</b> side effects of all statins:</p> <ul style="list-style-type: none"> <li>• Muscle pain is the most common side effect caused by statin use. Several studies found that over 10% of people taking high-dose statins had muscle pain.</li> </ul> <p>Symptoms could be:</p> <ul style="list-style-type: none"> <li>• unusual muscle pain or cramps</li> <li>• tiredness</li> <li>• fever</li> <li>• dark urine</li> <li>• Diarrhoea.</li> </ul> <p>These could be symptoms of <b>rhabdomyolysis</b>, a dangerous muscle condition that can cause kidney problems.</p> <p><b>Rare</b> side effects of all statins:</p> <ul style="list-style-type: none"> <li>• memory loss or confusion</li> <li>• increased blood sugar, which can lead to diabetes</li> <li>• kidney or liver damage.</li> </ul>

Figure 4 - The side effects of metformin and statins

### Berberine

Berberine (BBR) is an isoquinoline alkaloid found in plants belonging to the *Berberidaceae*, *Ranunculaceae* and *Papaveraceae* families and is widely used in Ayurvedic and Chinese medicine [42]. Recent research has clearly shown that BBR possesses various pharmacological activities that have applications in a wide spectrum of therapeutic areas where it has shown enormous potential, including cancer. However, a major disadvantage of BBR is its poor oral bioavailability which is attributed mainly to a P-glycoprotein (P-gp)-mediated gut extrusion process [43]. However, several strategies have been proposed to improve its activity. The amount of BBR crossing enterocytes seems to be reduced by approximately 90% by P-gp, which suggests its clinical effectiveness could be improved either by the use of a P-gp inhibitor or by chemical modification of BBR allowing it to overcome P-gp antagonism [44]. A good candidate among potential P-gp inhibitors is silymarin from *Silybum marianum* owing to its very high safety profile [45]. A combination of BBR and silymarin has shown greater clinical effectiveness in reducing cholesterol and glycaemia than BBR extract alone [46] and has proven efficacy in both diabetic and non-diabetic patients.

BBR has been shown to regulate both glucose and lipid metabolism in vitro and in vivo, and so could be administered alone or together with other nutraceuticals or conventional drugs to manage metabolic disorders associated with increased cancer risk and progression. BBR has various mechanisms of action. In hypercholesterolaemia, the pro-

tein convertase subtilisin/kexin type 9 (PCSK9) is a key regulator of cholesterol homeostasis that controls low-density lipoprotein (LDL) receptor (LDLR) density on the surface of hepatocytes [47]. Consequently, inhibition of PCSK9 would be a safe and cost-effective method to efficiently lower plasma LDL cholesterol, non-HDL cholesterol and lipoprotein. BBR in particular has shown good LDL-lowering activity, increasing the uptake of LDL cholesterol by enhancing the stability of its hepatic receptor. However, the fact that it has a different mechanism of action than statins allows it to be combined with statins in order to increase treatment efficacy [48].

Moreover, in the glycaemic setting, BBR has demonstrated its effectiveness in diabetic patients, significantly decreasing fasting and postprandial blood glucose and glycosylated haemoglobin (HbA1c) levels. Interestingly, its effect (but not its mechanisms of action) is similar to that of metformin [49]. BBR regulates glucose metabolism by stimulating glucose uptake by glucose transporter type 4 (GLUT-4) upregulation, and activating 5' adenosine monophosphate-activated protein kinase (5' AMPK) as a consequence of inhibition of mitochondrial function. These different mechanisms mean BBR can be combined with other glucose-lowering agents [50] in order to increase efficacy without increasing side effects. Several studies have confirmed its efficacy. A recent systemic review and meta-analysis of RCTs showed that administration of BBR produced a significant reduction in levels of total cholesterol (-25%), triglycerides (-20%) and low-density lipoprotein cholesterol (-30%), with a remarkable increase in HDL [51]. No serious adverse effects of berberine were reported and the authors concluded that BBR may have beneficial effects for the control of blood lipid levels.

A systemic review and meta-analysis of RCTs also showed that BBR was effective for treating hyperglycaemia, demonstrating significant reductions in several glycaemic parameters such as fasting plasma glucose levels (FPG), postprandial plasma glucose levels (PPG) and HbA1c. Moreover, compared with oral hypoglycaemic drugs alone, BBR administered with the same oral hypoglycaemics showed better glycaemic control. No serious adverse effects from BBR were reported [52].

These data indicate that, compared with other first-line drugs, BBR has a comparable therapeutic effect on hyperlipidaemia, hyperglycaemia, and IR and no serious side effects. Considering the relatively low cost, BBR might be a good alternative for low socioeconomic status patients for treating metabolic disorders over a long period of time.

### Curcumin

Curcumin is another promising compound active against the pathways associated with metabolic disorders and another good alternative to conventional agents usually used in this setting. Curcumin (diferuloylmethane) is an active component of turmeric derived from the rhizome of *Curcuma longa*. Turmeric is a dietary spice and a colouring agent, but several preclinical and clinical studies have demonstrated that curcumin has both preventive and therapeutic significance in many diseases including cancer [53].

Clinical trials have shown that curcumin is safe in humans but has poor bioavailability. Low plasma and tissue levels of curcumin appear to be due to poor absorption, fast metabolism and rapid systemic elimination. However, use of adjuvants such as piperine (which interferes with glucuronidation), liposomal curcumin, curcumin nanoparticles or the curcumin–phospholipid complex can improve its bioavailability [54].

Research over the last few decades has shown that curcumin exerts its anticancer activity on a wide range of molecular targets. It influences multiple signalling pathways and regulates the expression of several transcription factors, inflammatory cytokines, enzymes, growth factors, receptors, adhesion molecules, anti-apoptotic proteins and cell cycle proteins [55]. However, its anticancer activity in metabolic conditions is based on its strong anti-inflammatory and antioxidant activity and its ability to reverse IR. The beneficial and anti-inflammatory effects of curcumin and curcuminoids in the obese state are produced through regulation of a diverse range of molecular targets. The anti-inflammatory effect of curcumin is most likely mediated through its ability to downregulate cytokines (such as TNF- $\alpha$ , IL-1 and IL-6) and to inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX) and inducible nitric oxide synthase (iNOS) which are important enzymes mediating inflammatory processes. Moreover, curcumin is particularly active against NF- $\kappa$ B, a transcription factor that regulates the expression of genes involved in controlling cellular proliferation/growth and inflammatory responses [56]. Because inflammation, particularly obesity-related subclinical inflammation, is closely linked to tumour promotion, curcumin with its potent anti-

inflammatory properties is anticipated to exert chemopreventive and therapeutic effects on carcinogenesis related to metabolic disorders.

Experimental studies suggest curcumin is also an effective antidiabetic agent without serious side effects [57]. The impaired insulin sensitivity seen with obesity is thought to be due to the presence of high concentrations of free fatty acids in plasma and tissues [58]. The lipid-induced IR in obesity is mainly due to the free fatty acid-mediated activation of NF- $\kappa$ B and other signalling pathways. The potential mechanisms modulated by curcumin to influence IR have been clarified by several experimental and clinical studies. They suggested that curcumin acts through four pathways to reduce IR and its comorbidities by improving glucose homeostasis, lipid metabolism, the insulin pathway, oxidative stress and inflammation. This highlights its potential for use as adjuvant treatment in obesity, metabolic syndrome, prediabetes, diabetes, cardiovascular disease and cancer. Moreover, recent studies have shown that curcumin can inhibit 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD-1), an enzyme expressed in abdominal subcutaneous fat and the liver in overweight/obese subjects. This enzyme is key for the conversion of cortisone to cortisol and consequently the induction of IR [59]. A recent randomized, double-blind, placebo-controlled trial reported that a 9-month curcumin intervention in a prediabetic population significantly lowered the number of prediabetic individuals who developed type 2 diabetes. In addition, curcumin treatment appeared to improve the overall function of  $\beta$ -cells, with very minor adverse effects [60].

### Conclusions

Metabolic disorders are a group of symptoms and conditions closely related to obesity and overweight which are recognized as emerging worldwide health problems. They are of increasing concern because of their major effects on morbidity, mortality and costs. These conditions are risk factors for many common diseases, including cancer, particularly tumours with a hormonal aetiology. Metabolic disorders are often reversible with prompt therapeutic interventions which should therefore be implemented to prevent and treat cancer. Drugs commonly utilized for metabolic disorders have shown good efficacy but also have side effects which limit compliance. There is an urgent need to find alternative or synergic compounds with similar efficacy but no side effects. Among several nutraceuticals, berberine and curcumin in particular have an excellent safety profile and have shown good efficacy against metabolic disorders. We believe they

are perfect alternatives which merit further study and introduction into clinical practice.

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