Review Paper:

Capsaicin (*Capsicum Annuum*): A ubiquitous compound with multivarient pharmaceutical properties

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Abstract

India is the largest chili pepper (Capsicum annuum) producer, consumer and exporter in the world. It has been used routinely in the treatment of various human diseases by indigenous people since ancient times. Several natural compounds provide an interesting zone of research because of their low toxicity and potent efficacy. Capsaicin (methyl-N-vanillyl-6-nonenamide) is a bioactive phytochemical rich in chilli pepper and is also found in habaneros, jalapenos pepper and cayenne pepper. However, most research study has shown that capsaicin interposes with different types of pharmacological properties such as anticarcinogenic, antimutagenic, anti-inflammatory, anti-obesity and pain relief. In pharmacology it works by activating the TRPV1 channel.

Although many endogenous and exogenous agonists select the receptor, capsaicin itself is the most potent and selective agonist. TRPV1 activation triggers depolarization by influx of sodium and calcium ions leading to sensations of burning, itching or stinging. Capsaicin, while burning fats, relieving topical pain and reducing insulin spikes in diabetes, was confirmed to have benefits in increasing metabolism. In cancer, Capsaicin can induce apoptosis, prohibits cancer cell proliferation, angiogenesis and metastasis via TRPV1, CDKS, VEGF and NF-κB ligands. In this review, we highlight the pharmacological properties of capsaicin and its emerging role in cancer.

Keywords: Chilli pepper, Phytochemical, Capsaicin, Cancer.

Introduction

Medicinal plants are natural strength for human life to promote a healthy disease-free life[31]. It is a part of human culture to fight against illnesses[22]. The quest to develop pharmaceutical properties from natural sources includes a long history and significant success stories. In drug development, phytochemicals and ubiquitous bioactive compounds participate in significant role[29] because of their broad abundance of fruits and vegetables. They are a crucial role of the human diet and have attracted significant interest as prospective chemotherapists[30]. Chilli pepper is a documented species of *capsicum annuum* 7000 years' old[32]. Due to their unique pungency, peppers are primarily consumed as food. They have rich nutritional properties, are a strong source of vitamins C and E, Provitamin A, carotenoids and antioxidants[19,27]. Generally chilli pepper that accumulate within the placenta of maturing Capsicum (chilli pepper pods) has wide applications in food, medicine and pharmacy. Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a natural alkaloid and the active main ingredient of chilli pepper.

This compound was initially isolated in 1816 that is partially refined crystalline shape by Bucholz and the pure crystalline was formed by Thresh and named it capsaicin (CAP). Chilli pepper displays anti-inflammatory and analgesic properties and CAP creams and lotions are mostly prescribed for the medical care of neuralgia, arthritis and muscle pain[38]. CAP was used to treat pain and inflammation associated with neuropathic pain conditions such as rheumatoid arthritis, cluster headaches, herpes zoster and vasomotor rhinitis. The specific application of CAP is anti-carcinogenic and anti - tumorigenic properties.

Nowadays, the most recent study focuses on the chemical and chemotherapeutic effects of CAP, which reduce the growth of various human cancers such as liver, lung, colon, pancreas, stomach, prostate, leukocyte, breast, esophagus and tongue cancer[15]. Although evidence accumulates that CAP modifies various markers of cancer and prevents testicular cancer in various animal models, several recent surveys reveal the ability of the compound to induce apoptosis, promote cell cycle arrest, angiogenesis and metastasis. The CAP and other vanilloids are up to now regularly found in the diet and prove that they are safe to eat. It is also possible for cancer patients or those at risk of developing cancer, to eat a diet and prevent the disease such as anti-obesity, pain relief, asthma, gastric disorder, urological disorder. This review highlights the impact of CAP on physicochemical, pharmaceutical properties and cancer mechanism pathways (TRPV1, CDKS, VEGF and NF-κB).

Physicochemical properties of capsaicin: CAP is a natural alkaloid and the most pungent ingredient of hot peppers (Capsicum) is also known as trans−8-methyl-N-vanillyl-6-nonenamide[13]. It belongs to the vanilloid connection of compounds like vanilla, bay leaf and clove eugenol, ginger gingerbread and hot pepper CAP. The vanilloids have a moiety of vanillyl (4-hydroxy-3-methoxybenzyl) which gives their biological activity. CAP features a benzene ring and a long hydrophobic carbon tail with a polar set band (Figure 1). This chemical compound is crystalline, off-white

solid, lipophilic, colorless and odorless. It has a melting point of 62–65°C and is soluble in ethanol, acetone and fatty oils, although not water-soluble and having 305.4 kDa molecular weight. The molecular formula is $C_{18}H_{27}NO_3$. CAP and dihydrocapsaicin comprise 80–90% of the capsaicinoids found in peppers in concentrations of 0.1–1.0% and in a ratio of 1:1–2:1 respectively[12].

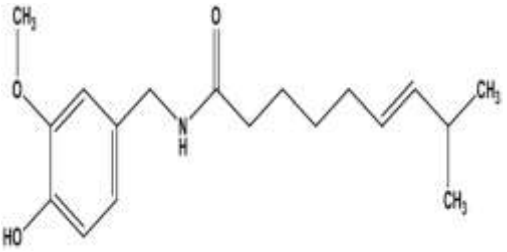

Figure 1: Structure of capsaicin

There are several experimental methods for capsaicinoid analysis ranging from colorimetric photometry, liquid and gas chromatography, mass spectrometry, nuclear magnetic resonance, spectroscopy, amperometry, modified capillary electrophoresis and olfactory electronic sensing. CAP is known to be effectively absorbed topically from the skin. Half-life of CAP is about 24 hours and the metabolism is apparently similar in human, rat and dog microsome[37].

Pharmacological effects of capsaicin: Chilli pepper CAP can deter cancer, heart disease, stroke, blood clots, obesity, blood pressure, cholesterol, stomach ulcer, coughs, colds and is also useful for kidneys, spleen, pancreas, lungs and heart[33]. The pharmacological effects of CAP are shown in figure 2. Obesity is an speed up public health problem globally and a major risk factor as it is related with chronic inflammation and metabolic disorder, a cluster of morbidities that includes hypertension, hyperlipidemia and type 2 diabetes mellitus[17]. It can increase the risks of developing serious health problem such as cardiovascular diseases, chronic kidney disease and stroke[21].

In the past decades, several studies have proven that CAP is effective in promoting weight loss[45]. Chilli blend promotes specific energy-burning receptors in fat cells. TRPV1 (transient vanilloid receptor potency 1) receptors, which are present in large amounts in fat cells, may burn energy rather than store these fat cells. Numerous epidemiology and animal studies have proven that CAP, as an agonist of TRPV1, can be a promising strategy for treating or preventing obesity.

While it is well known that the activation of the TRPV1 receptor triggers much of the effect, the process of action is not entirely understood at present. TRPV1 plays an important role to controlling metabolic health throughout the body including body weight, glucose and lipid metabolism and the cardiovascular system[7]. Lejeune et al[25] research studies have reported on CAP's effects on people's weight loss.

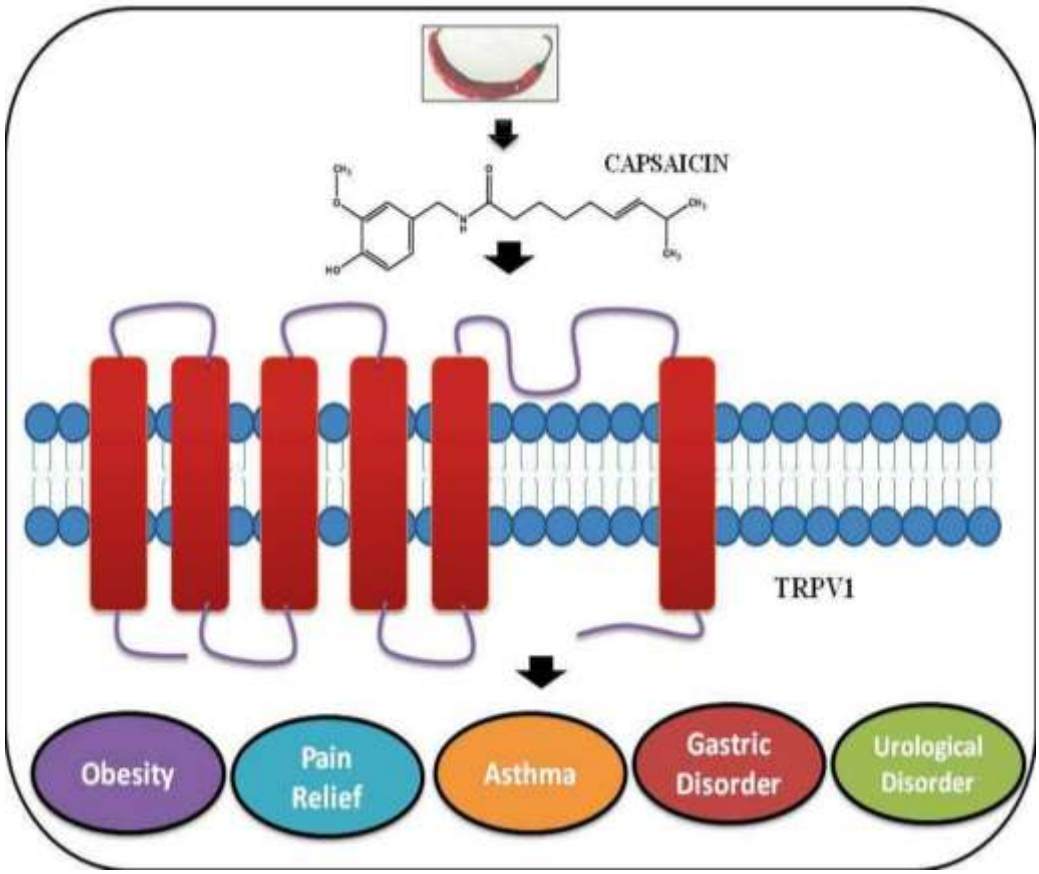

Figure 2: Pharmacological effects of CAP

Topical CAP formulations are used for pain management. It has played a crucial role in folk medicine. CAP may be lipophilic with little affinity for the aqueous blood phase and is readily absorbed into the epidermal and dermal layers[3]. The first systematic report on the pain reducing power of topical CAP in the West came out in 1850 as an advice for the use of a chilli pepper extract. CAP is used to alleviate muscle and joint pain, induces strains, sprains, inflammation, swelling, or backaches in medicated creams. Gel is also used to treat nerve pain (neuralgia).

The Topical CAP has shown analgesic advantages in postherpetic neuralgia, painful polyneuropathies such as diabetic and HIV-related neuropathy and postmastectomy/surgical neuropathic sickness[14]. Some research encourages that it can help improve psoriasis scaling, inflammation, redness and pain[2]. Applied topically to human skin, CAP induces itching, stinging, burning sensations or cutaneous vasodilatation followed soon by warmth and mechanical stimulation hyperalgesia.

The primary mechanism by which CAP goes for to reduce pain is to eliminate B, a neuropeptide involved in transmitting pain signals to the brain from nerve endings and activate inflammatory cytokines in the joints. Local nociceptive function is eventually inactivated and pain relief occurs. The CAP works by activating the channel TRPV1. Most endogenous and highly selective and effective (low nanomolar affinity) exogenous agonist for the TRPV1 receptor activate the channel, A complex trans-membrane receptor-ion channel combines temperature, pH and endogenous lipid responses[1].

Asthma is narrow airway condition and excessive mucus is created by swelling. This can make breathing difficult and cause coughing, wheezing and shortness of breath. Chronic cough is one of the high widespread signs of chronic asthma patients. CAP, the active constituent of red chili pepper, is commonly used as a stimulant for cough receptors and is believed to provide cough mainly by stimulating C-fibre endings. The ingredient that gives their flame to red peppers is promising to help people with asthma breathe easier, wheeze less and usually feel better. It has gained favour as the annoying agent of choice to measure cough reflex sensitivity.

First, the drug, CAP, activates and then blocks tiny nerves that may cause coughing, shortness of breath and other symptoms of asthma. CAP has also been commonly used as a diagnostic tool for asthmatic patients, since the risk of CAP evokes hypersensitivity in the airways[9].

Gastric mucosa integrity depends on the balance between militaristic and protective influences. The failure of this equilibrium causes gastric disorders to evolve[23]. As a causative factor, helicobacter pylori increase the risk of developing human gastrointestinal disorders such as acute gastritis, chronic gastritis, gastro-duodenal ulcer, lymphoma of the lymphoma of the gastric mucosa and gastric adenocarcinoma. It was also involved in iron deficiency anemia and extra-gastrointestinal disorders such as atherosclerosis, ischemic heart disease and stroke[46].

Such GI (Gastro intestinal) condition may be in sub-categories of oesophageal, gastroduodenal, bladder, biliary, anorectal and abdominal pain depending on the rome diagnostic criteria. Recent research has shown that rutaecarpine's pharmacological effects are related to endogenous calcitonin-related peptide (CGRP) release stimulation through the activation of vanilloid receptors in CAP-sensitive sensory nerve and is one of the defensive mechanisms. CAP-sensitive afferent nerves have a non-selective cation channel known as CAP receptor or transient vanilloid 1 potential receptor (TRVP1).

This receptor is not only responsive to CAP and other vanilloids, but also to protons, noxious heat and endogenous ligands such as anadarmide, n-oleodopamine and lypoxygenase products[20]. Chili pepper compounds play an important role in the defence of the gastric mucosa by preventing drug-induced mucosal injury in animals and by reducing the amount of indomethacin (IND) mediated in healthy humans.

Urological disorders are kidney and urinary tract diseases. Neurogenic bladder (NGB) or bladder dysfunction can result from any neurological insult that interferes with the normal functioning of the lower urinary tract requiring intact pathways involving neurological central and peripheral systems. The human bladder contains sensitive nerves of CAP. There are many causes of NGB, but most commonly include spinal cord injury, multiple sclerosis, spina bifida, spinal degenerative disease, cerebrovascular accident and peripheral bladder innervation surgical extirpatory procedures.

Vanilloids are compounds containing vanillyl group including vanillyl alcohol, vanillin, vanillic acid, homovanillic acid, CAP and capsaicinoids. Vanilloids bind to the transient receptor potential vanilloid type 1 (TRPV1) receptor (an ion channel which responds naturally to noxious stimuli such as high temperature and acidic pH). CAP reduced the number of day by day urinary incontinence[10].

Capsaicin and cancer

Cancer is the preceding cause of death in developed and developing countries. Chemoprevention relates to the use of natural, synthetic or biological substances for cancer reversal, suppression or prevention[41].Searching for new antitumor agents from plant sources could be a sensible and promising approach which may lead to discover the novel anti-cancer or anti-tumor drugs[36].

CAP is a naturally found phenolic constituent that is contained in red chilli pepper. This compound has recently received fair attention due to its chemical protective

properties against certain cancers. CAP has powerful preventive and therapeutic effects against many types of cancers including lung cancer, breast cancer, skin cancer, colon cancer, prostate cancer, pancreatic cancer, bladder cancer.

A number of different studies have proved that CAP can inhibit the carcinogenic or mutagenic processes *in vitro* and *in vivo*. CAP consumption can decrease the hazard of cancer in humans. The anticancer activity of CAP has been widely reviewed for a variety of cancers, however, the effect on carcinogenesis remains controversial due to conflicting results in epidemiological and basic research studies.

CAP has been confirmed by most laboratories to have chemopreventive and chemotherapy effects[44] and a variety of *in vivo* studies using rodent models support anticarcinogenic activity of CAP[35]. However, CAP may act as a carcinoma and co-carcinoma[43]. The suggested anticancer mechanisms (Figure 3) of CAP include an increase of cell-cycle arrest, apoptosis and angiogenesis. CAP's ability to suppress the growth of cancer cells through induction of apoptosis is excellent.

Furthermore, activation associated with CAP -induced anti-cancer effects includes arrest of cell cycle progression, inhibition of transcription factor expression and suppression of growth signal transduction pathways[26]. The arrest of the cell cycle growth or development as a defence mechanism against various cancers and cancer prevention has gained a lot of interest. Angiogenesis is a complex process that involves extracellular matrix degradation, proliferation and migration. Therefore, CAP interferes with common angiogenesis signalling pathways and may have the potent to prevent cancer from become malignant tumor or tumorigenesis.

Apoptosis: Apoptosis is an important barrier to the progress of cancer and is closely associated with the loss of apoptotic signals[11]. The intrinsic mitochondrial death pathway and the extrinsic death receptor pathway are two main signals that cause performer / effector caspases and contribute to programmed cell death. Some proteins involved in the mitochondrial death pathway have been allowed to target CAP to induce apoptosis in various cancer cell lines. Once CAP enters a cancer cell, it binds to the surface of the cell and links to a cell receptor, a protein that is expressed / produced on the surface of the cell, called TRPV1.

The TRPV1 receptor is a calcium / sodium channel that controls the cancer cell's entry and exit. CAP is converted to TRPV1 and is transmitted to the cancer cell overdrive when self-destruction is initiated by induced apoptosis. For example, CAP treatment triggered the differentiation cluster 95 (CD95)-mediated intrinsic and extrinsic apoptotic pathways and suppressed antiapoptotic protein expression, B-cell lymphoma 2 resulting in caspase-9 and -3 activation, loss of mitochondrial membrane potential and subsequent cytochrome c release increases[18]. Both mechanisms support the hypothesis that by activating multiple pathways, CAP induces apoptosis in cancer cells.

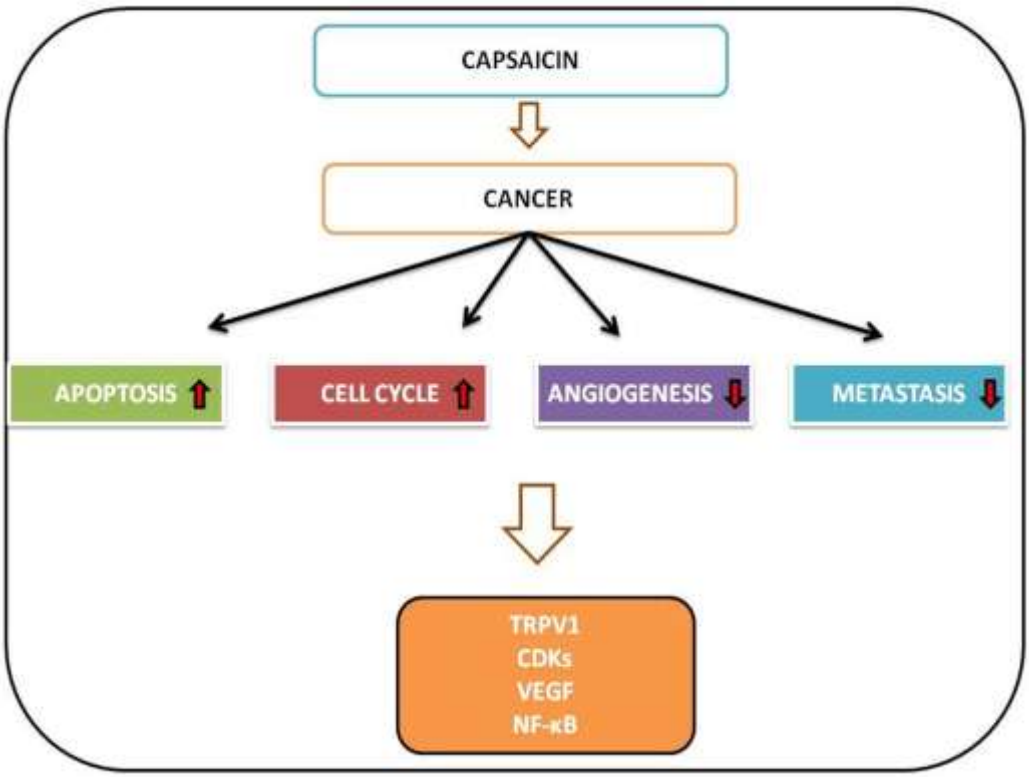

Figure 3: Anticancer mechanisms of CAP

Cell cycle arrest: Cell cycle is a series of cell replication events. Transferring genetic information from one generation of cells to the next involves gene replication during the S process and the division into two new daughter cells during mitosis or M phase. S-phase and M-phase are critical processes rigorously organized in a cyclic cycle that allows the proper replication of the cell without any genetic abnormalities[16].

Some alteration in these pathways will increase cancer risk. Cyclins, cyclin-dependent kinases (CDKs) and CDK inhibitors are essential components of the cell cycle machinery. When triggered, the CDKs provide the cells with a driving force to travel from one stage to the next, but if cyclin and/or CDKs are disrupted, the cell cycle is arrested[6]. The cell cycle and growth arrest have gained significant attention as a cancer defence mechanism and a strategy for cancer prevention and treatment, as well as homeostasis of the tissue. Chen et al[6] found that CAP inhibits the proliferation of bladder carcinoma cells by growth arrest with the inhibition of CDK2, CDK4 and CDK6.

CAP is a new modulator of the receptor epithelial growth factor pathway and suppresses strong growth of both receptor-positive and negative breast cancer cells[40]. It has considered a novel anti-androgenic receptor drug in prostate cancer. On the other hand, CAP was found to have divergent effects on the growth of gastric cancer cells depending on the status of tumor-associated NADH oxidase expression[42]. Taken together, these data show that by targeting cell cycle regulators, CAP can stop the growth and division of cancer cells.

Angiogenesis: Angiogenesis is the development of new vessels of the blood. However, angiogenesis is a pre-requisite for cancer progression due to the lack of oxygen and other mandatory nutrients that cancer tissues cannot grow beyond a certain size (generally 1 to 2-mm in diameter). It is a complicated process involving the degradation and proliferation of extracellular matrix, migration and morphological differentiation of endothelial cells into channels. Many factors control the process such as growth factors and cytokines, but the vascular endothelial growth factor (VEGF) was the research focus due to its key role in angiogenesis[8].

CAP has *in vitro* and *in vivo* anti-angiogenic effects. CAP's antiangiogenic effects mechanisms include inhibition of VEGF-induced cell proliferation, DNA synthesis, chemical motility, capillary tube formation and sprouting of vessels[28]. VEGF is one of the angiogenic process molecular switches while CAP was documented to increase DNA binding and VEGF formation in human melanoma (A375P and A375SM) cells with hypoxia-inducible factor-1a (HIF1α)[34]. A subsequent study showed that CAP reduced the growth of human multiple xenograft myeloma cells by reducing VEGF expression[4]. CAP's inhibition of VEGF expression and antiangiogenic activity in human non-small cell lung cancer was mediated by stabilization of p53 by upregulation of scaffold matrix-associated region-1 (SMAR1)-binding protein and subsequent degradation of HIF1a. CAP -induced SMAR1 also resulted in repression of COX-2 activity and the production of PGE2, thus blocking nuclear localization and transcriptional activation of HIF1a[5]. CAP therefore interferes with specific angiogenic signalling pathways and may have the potential to prevent malignancy of cancer.

Metastasis: Metastasis is a complex and multi-stage process that occurs when cancer cells become capable of invading the vasculature and migrating to distant organs. Metastatic cancer is therapy-resistant and causes 80% of deaths from cancer and remains a major challenge in cancer therapy[39]. Several studies have shown CAP's ability to block migration and invasion of specific cancer cells. The anti-migration and anti-invasive effects of CAP on cholangiocarcinoma (HuCCT1) cells were mediated by inhibition of MMP-9 expression and activation of NF-κB through induced AMPK phosphorylation and SIRT1 activity induction[24].

CAP, however, greatly prevented the movement of melanoma cells without contributing to strong cell cytotoxicity. This effect was associated with down-regulation of the signalling cascade of phosphoinositide 3-kinase (PI3 K) and reduction of RAS-related c3 botulinum toxin substrate 1 (RAC1), which is a key kinase controlling motility and migration of cells. Chen et al[7] demonstrated that CAP diminished tNOX expression and attenuated phosphorylation of ERK, paxillin and focal adhesion kinase, thereby blocking migration of human TSGH and T24 bladder cancer cells. Report shows CAP elevated E-cadherin and decreased the level of Ncadherin, indicating that epithelial to mesenchymal transformation can be suppressed[7].

Conclusion

This review covers natural capsaicin lead compounds and their broad pharmacological properties and methods for identification according to their official pharmacopoeias. Natural CAP is of great interest because of its wide range of pharmacological properties and it attracts many clinical chemists to further spinal derivatives and screen them as multiple novel therapeutic agents. There are plenty of health advantages to the tiny quantity of chilli in our daily diet.

Many scientists have researched on the medicinal impacts of CAP; this evaluation will offer fresh impetus to the use of CAP in different disorder. CAP can be used to treat inflammatory diseases, various kinds of infections and many chronic diseases including cancer.

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