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The effectiveness and mechanism of action of N-acetylcysteine in cancer

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ABSTRACT

Introduction: N-acetylcysteine (NAC) is a sulfhydryl substance, a derivative of the amino acid L-cysteine, exhibiting high antioxidant properties. NAC is currently used as a mucolytic and antidote to acetaminophen and as an antioxidant in chronic diseases caused by oxidative stress. Although cancer is characterized by high level of ROS and increased oxidative stress, its use in the treat-ment of this disease is controversial. Due to varying research results, there is ongoing scientific debate whether or not NAC may be effective in treating cancer.

Material and methods: In order to search for scientific articles, the PubMed database was used with the following keywords: N-acetylcysteine, cancer, cancer metastases, antioxidant treatment, mechanism of action, ROS, antioxidant, tumor angiogenesis, antioxidant therapy.

Results: NAC supplementation can reduce tumor cell proliferation, migration, and invasion in various types of cancer. NAC reduces toxicity caused by chemotherapy and radiotherapy in the course of cancer therapy and exerts a preventive effect, hampering the development of cancer. However, caution should be exercised when using NAC in cancer patients, especially with regard to metastases, as NAC was reported to intensify them in some studies. Thus, the results of using NAC in humans may depend on the stage of cancer. Moreover, the reason for the various effects of NAC in cancer treatment seems to be the involvement of this drug in the modulation of signaling pathways that can induce or inhibit cancer.

Summary: The use of NAC in cancer treatment results in outcomes ranging from beneficial to harmful, mainly because ROS can mediate both cancer-promoting and cancer-inhibitory signalling. Negative NAC results were mainly related to metastasis. The effect of NAC may depend on whether the type of cancer depends on ROS signalling for its survival and metastasis. Further research is needed to resolve the role of NAC in cancer treatment.

INTRODUCTION

Reactive oxygen species (ROS) play an important role in physiology, but in large amounts they can lead to oxidative stress. Oxidative stress occurs when ROS levels are excessive and antioxidant levels are relatively scare. ROS in large doses can cause oxidative damage to molecules such as nucleic acids, proteins, lipids, glucose, and consequently the destruction of enzymes and damage to structural protein membranes, gene mutation, and even pro-oncogenic signaling activation. The pathogenesis of several serious human diseases, including cancer, is related to oxidative stress (Radomska-Leśniewska, 2017). Increased oxidative stress can initiate tumor development and cause cancer progression through direct oxidation of macromolecules or aberrant redox signaling (Luo, 2011). Since oxidative stress plays an important role in carcinogenesis and cancer progression, the use of antioxidants to modulate ROS levels in cancer treatment is warranted (Hayes, 2020; Klaunig, 2018). Modulating ROS levels is a promising anticancer strategy and enables the inhibition of carcinogenesis and tumor development induced by oxidative damage and ROS-dependent cell death (Poprac, 2017; Forman, 2021).

N-acetylcysteine (NAC) is a synthetic antioxidant and has strong direct and indirect antioxidant effects. NAC is currently used mainly as a mucolytic and antidote to acetaminophen and as an antioxidant in chronic diseases caused by oxidative stress including lung diseases, cardiovascular diseases, kidney diseases, liver diseases, infectious diseases, psychiatric illness. Although cancer is characterized by increased oxidative stress, the use of NAC in cancer treatment is controversial. Due to varying study results, this review discusses whether NAC can be effective and safe in the treatment of cancer (Tenorio, 2021).

SEARCH STRATEGY AND SELECTION CRITERIA

The aim of the work was to collect data about the mechanism of action of N-acetylcysteine, determine the effectiveness of NAC application in cancer, and safety of using this drug. The authors reviewed information from original articles published up to 2023. The articles were searched in the PubMed database, using the following keyword: N-acetylcysteine, cancer, cancer metastases, antioxidant treatment, mechanism of action, ROS, antioxidant, tumor angiogenesis, antioxidant therapy. Manually selected materials related to the topic were added.

RESULTS

ROS AND OXIDATIVE STRESS

ROSs are natural products of the oxygen metabolism of the cells (Augustyniak, 2010). During cellular metabolism in mitochondria, molecular O_2 is converted into H_2O in the oxidative phosphorylation process resulting in ROS generation: superoxide radical (O^{2-} •), hydrogen peroxide (H_2O_2), and the hydroxyl radical (• OH). H_2O_2 is also produced by peroxisomes (Rushworth, 2014).

The level of ROSs depends on both endogenous ROS formation and exposure to exogenous ROSs. The impact of ROS on physiology depends on their concentration. A low level of ROS is necessary for the proper functioning of the organism. They participate in gene expression modulation, intracellular signal transduction, cell proliferation, transcription, and apoptosis (Ushio-Fukai, 2008; Polsjak, 2013), as well as Ca^{2+} circulation and protein phosphorylation. ROS at a low level activates some transcription factors, including nuclear factor κB (NFκB) or activator protein 1 (AP-1) (Ushio-Fukai, 2008). The proper course of inflammatory and angiogenesis processes also depends on ROS (Bir, 2013; Nijmeh, 2010). ROS in high levels act to detriment the body, being cytotoxic and mutagenic to cells, leading to apoptosis and cell death (Manea, 2010). The body's defense against ROS toxicity is provided by antioxidants, substances that neutralize free radicals or their actions.

Oxidative stress means an imbalance between the level of ROS production and antioxidant mechanisms). It leads to disorders of cellular metabolism and biological functions of cells and the organism, as a result of damage of cellular elements, including: DNA, proteins and lipids (Rushworth, 2014; Ames, 1993).

Many transcription factors can be induced by oxidative stress. One of them is nuclear factor erythroid 2-related factor 2 (Nrf2), which regulates the expression of molecules performing antioxidant functions in the cell (Gorrini, 2013). Nrf2 protects cells against oxidative or electrophilic stress by activating downstream target genes and enzymes such as heme oxygenase 1 (HO-1), NAD(P)H oxidase 1 (NOX1), NAD(P)H quinone oxidoreductase 1 (NQO1), glutamate cysteine ligase catalytic subunit (GCLC), glutamate ligase modifier subunit cysteine (GCLM), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Suzuki, 2017). The antioxidant defense system, in addition to the these enzymes, include vitamin C and vitamin E, thiols or sulfhydryl-containing compounds such as glutathione (GSH) and thioredoxin. GSH contains a free sulfhydryl group, thanks to which it has an antioxidant effect and is a source of reducing equivalents that remove harmful ROS (Rushworth, 2014). In addition to its antioxidant effects, GSH exerts a positive effect through protein thiolation, drug detoxification, and regulation of signal transduction modulated by oxidation-reduction reactions (Frye, 2019, de Andrade, 2015, Rushworth, 2014).

ROS IN CANCER

Cancer cells produce high levels of ROS which participate in the generation of oxidative stress leading to abnormal redox signaling. Oxidative stress in turn, may contribute to the development of cancer. Increased oxidative stress in cancer cells is responsible for the glycolytic and catabolic state. Catabolites, including lactate, are released there supporting mitochondrial metabolism through mitochondrial heterogeneity (Martinez-Outschoorn, 2016). Mitochondrial heterogeneity contributes to the increase of oxidative stress in cancer cell, their proliferation, tumor growth, and metastasis (Dhouib, 2016).The increased levels of ROS exert various effects on cancer cells. On the one hand, in huge amounts, they produce anticancer effects through oxidative damage and ROS-dependent death signaling. ROS increases gene mutation and pathological inflammation by directly oxidizing macromolecules such as nucleic acids, proteins, lipids and glucose (Zhong, 2015). On the other hand, lower levels of ROS play a key role during tumorigenesis and promotes cancer cell proliferation and cancer progression. Cancer ROS, especially H_2O_2 and $O^{2\cdot-}$, can act as signaling molecules, causing malfunction of various signaling pathways. In cancer cells ROSs are involved in upregulation of HIF-1α and VEGF protein expression through activation of PI3K/Akt/p706K pathway or MEK/ERK pathway (Ushio-Fukai, 2008). The high level of VEGF and MMP9, stimulated by NOX 1, is a characteristic feature of cancer cells. Therefore ROS induces angiogenesis in tumor which contribute to their development as well (Radomska-Leśniewska, 2016).

N-ACETYLCYSTEINE

NAC contains the amino acid L-cysteine (with sulphhydryl group) and acetyl group attached to the amino (NH_2) group and it possesses high antioxidant capacities. It was first introduced as a mucolytic drug in respiratory diseases (e.g. cystic fibrosis) in 1963. Then it was used in paracetamol poisoning. In cancer

biology and immuno-oncology, NAC was used as a direct scavenger of reactive oxygen species (especially hydrogen peroxide) and as an antioxidant. NAC is safe and well tolerated, even at high doses (Ooi, 2018). It can be administered orally, intravenously, and by inhalation. After oral administration, its maximum plasma concentration (C_{max}) occurs up 2 hours (Dodd, 2008). NAC crosses the membrane and crosses the blood-brain barrier, depending on the dose and method of administration (Hara, 2017). The effects of NAC are attributed to its thiol modulation in cells (Aldini, 2018; Bansal, 2018; Cheng, 2023). The main products of NAC metabolism after complete metabolism, are cysteine, cystine, inorganic sulfate, and glutathione (Prescott, 1989). The bioavailability of NAC is approximately 10% and only a small amount reaches the plasma and tissues (Ezerina, 2018). After intravenous administration of NAC at a dose of 150 mg/kg over 15 min, the C_{max} of NAC averaged 554 mg/l (De Andrade, 2015). Since the bioavailability of NAC is relatively low NAC is used in high concentrations in studies (Cheng, 2023).

MECHANISM OF ACTION

NAC may act through several possible mechanisms including its key role for the intracellular role in GSH biosynthesis, as well as its antioxidant function through nucleophilic character – an extracellular scavenger. L-cysteine availability in the cell is rate-limiting for GSH synthesis, and NAC is essentially a prodrug that is converted to l-cysteine. L-cysteine, a precursor of reduced GSH, is a major endogenous antioxidant (Sadowska, 2005). NAC activity increases the concentration of GSH within the cells so it is able to restore disturbed antioxidant levels. It is known that oxidative stress and inflammation can be the cause of diminished levels of GSH. That is why NAC can normalize the disturbed redox status of the cell and modulates redox sensitive cell signaling and transcription pathways (de Andrade, 2015).

Moreover, the high antioxidant properties of NAC are due to the sulfhydryl compound, which enables direct scavenging of ROS such as superoxide radical, hydrogen peroxide, and hydroxyl radical. NAC may also act as a direct scavenger of peroxynitrite or related pathways. As mentioned above, the role of ROS depends mainly on their quantity, small amounts are necessary and beneficial for the body, while too large amounts of ROS are toxic (Aldini, 2018).

It should also be emphasized that the effect of NAC may sometimes be opposite, i.e. it may have pro-oxidant properties as a result of the auto-oxidation process causing the formation of H_2O_2 in the presence of O_2 (Lee, 2011).

NAC was reported to inhibit several pro-inflammatory and antiapoptotic pathways such as nuclear factor kappa B (NFκB), p38 MAP kinase, SAPK/INK, c-Fos, c-Jun N-terminal kinase pathways, and cyclin inhibitors (Radomska-Leśniewska, 2010; Radomska-Leśniewska, 2016; Sadowska, 2005; Zafarullah 2003) (Fig. 1).

Therefore NAC has been shown to inhibit various anti-inflammatory cytokines such as interleukin 8 (IL-8), IL-6, and tumor necrosis factor α (TNF-α) (Radomska-Leśniewska, 2010; Radomska-Leśniewska, 2006; Maher, 2007). A reduction in collagen synthesis and fibroblast proliferation was also demonstrated by NAC (Ask, 2006) (Fig. 1).

Since cancer is associated with impaired, abnormally high angiogenesis, NAC may be a potential drug that normalizes this process. NAC has been proven to effectively reduce angiogenesis-induced vascular endothelial growth factor (VEGF) (Ushio-Fukai, 2002), endothelial cell invasion, and *in vitro* angiogenesis by inhibiting metalloproteinase (MMP) activity (Cai, 1999). These studies are consistent with the results of our group, in which we presented the inhibition of MMP9 and the pro-angiogenic intercellular adhesion molecule-1 (ICAM-1) by this drug (Radomska-Leśniewska, 2006; Radomska -Leśniewska, 2010). NAC inhibited the expression of the most powerful stimulator of angiogenesis – VEGF in ras-transformed cancer cells (Nijmeh, 2010). It is also known that the above-mentioned drug has a cytoprotective effect on endothelial cells (Aluigi, 2000) (Fig. 1).

The mucolytic effect of NAC consists of breaking the disulfide bonds of highly cross-linked mucus glycoproteins (mucins), thus reducing the viscosity of mucus (Aldini, 2018). As an antidote to acetaminophen poisoning, NAC restores the hepatic GSH pool depleted in the drug detoxification process. GSH, in turn, neutralizes the N-acetyl-p-benzoquinoneimine (NAPQI) – the harmful metabolite of acetaminophen, and scavenges reactive oxygen and nitrogen species (Aldini, 2018, Rushworth, 2014).

NAC IN CANCER STUDIES

The effect of ROS (peroxide and H_2O_2) on cancer has been shown to be concentration-dependent. As it was mentioned above at low levels, superoxide/H_2O_2 induces cell proliferation and promotes cancer formation and progression while high levels of ROS can be cytotoxic to cancer cells and inhibit metastasis. Therefore, the impact of antioxidants may also exert various effects on cancer. Antioxidants can generally inhibit the formation and progression of cancer but potentially may contribute to the development of metastases (Hayes, 2020; Gill, 2016).

NAC has been extensively studied, due to its unique biological properties, as an agent in the prevention and treatment of cancer, as well as an agent to counteract the effects of chemotherapy and radiotherapy.

THERAPEUTIC POTENTIAL OF NAC

NAC was reported to enhance cancer cell apoptosis, reduce catabolism, mitochondrial dysfunction, and inflammatory, and inhibits oxidative stress mediators (Dhouib, 2016). Lung cancer studies revealed NAC abilities to detoxify chemicals, scavenge radicals and protect against DNA damage. NAC combined with epigallocatechin-3-gallate (EGCG), the main green tea polyphenols, form an adduct that may enhance the killing of cancer cells (Lambert, 2008) (Tab. 1). Reports emphasize the dual role of ROS and GSH in cancer initiation and progression (Fendt, 2020; Bansal, 2018). NAC treatment was reported to alleviate of ROS in the tumor microenvironment in triple-negative breast cancer (Kwon, 2021) Table 1). NAC administered with IL-2 synergistically enhanced the level of GSH and thus increased the effectiveness of interleukin-2/lymphokine activating therapy (Yim, 1994). In a human pilot study determining the antiproliferative effects of NAC on breast cancer NAC markedly reduces monocarboxylate transporter 4 (MCT4) transporter proteins from being utilized to import energy as lactate to cancer cells. MCT4 is considered a marker of aggressive cancer behavior with poor overall survival. NAC administration was associated with reduced breast cancer cell proliferation, oxidative stress, and inhibition of breast cancer stromal cell metabolism (Monti, 2017) (Tab. 1). A study in a mouse model of melanoma showed that NAC pretreatment had a beneficial effect by blocking the formation of 8-oxoguanine in mouse skin after neonatal UV treatment and delaying the onset of melanoma (Cotter, 2007) (Tab. 1). Similarly, good results were obtained in a study of patients with a history of melanoma and/or atypical nevus, where NAC reduced oxidative stress and glutathione deficiency in nevus caused by UV radiation (Goodson, 2009). NAC in glioblastoma multiforme may prevent proliferation, migration, and invasion in an antioxidant-independent manner by modulating Notch2 signaling (Deng, 2019). In an oncogenic KRAS ^{G12D}-driven mouse model (increased NADPH oxidase and decreased NRF2), lung adenocarcinoma attenuation was associated with ROS suppression by NAC (Song, 2018). It was also reported that NAC sensitizes pancreatic cancer cells to gemcitabine (Qanungo, 2014). NAC inhibited prostate cancer cell growth and prevented adhesion and invasion to remote locations in prostate cancer cell study (Lee, 2011) (Tab. 1).

The results of studies on the effect of NAC on cancer at the metastatic stage are ambiguous. NAC was shown to inhibit lung metastasis by Tigar/null pancreatic cancer cells. Furthermore, mitochondrially targeted antioxidant mito-TEMPO inhibited lung metastasis of orthotopically injected MDA-MB-231 breast cancer cells in immunodeficient mice (Cheng, 2023) (Tab. 1). However in a mouse model of lung cancer NAC increases lung cancer metastasis (Breau, 2019; Gill, 2016) which was explained by the reduction of oxidative stress in metastatic tumors and development in distant places (Sayin, 2014) (Tab. 1). It was also shown that vitamin E and NAC enhanced cancer cell proliferation by reducing ROS and diminishing p53 in mouse and human lung cancer cells (Sayin, 2014). NAC cultured with human melanoma cells resulted in increased proliferation and migration (Piskounova, 2015) (Tab. 1). Moreover, NAC administered in drinking water enhanced metastasis spread in a murine melanoma model (Le Gal, 2015). Wiel et al. reported that NAC and vitamin E increase metastasis to the liver, kidney, heart, and rib cage of lung cells harboring oncogenic K- RAS^{G12D} (Wiel, 2019). These antioxidants increased metastasis by reducing the level of ROS and free heme, which led to the stabilization of the transcription factors BTB (Broad-Complex, Tramtrack and Bric a brac) and CNC1 homologs (BACH1), whose function is to increase glucose uptake, glycolysis, and lactate secretion via Mct1 (Wiel, 2019) (Tab. 1, Figure 1). BACH1 is considered to be one of the master regulators of metastasis (Lee, 2011) and increases the expression of metastasis-related genes such as MMP1, MMP3, CXCR4 (C-X-C chemokine receptor type 4), CTGF (Connective tissue growth factor), PGK2 (Phosphoglycerate Kinase 2), and ROBO1(Roundabout Guidance

Receptor 1) (Liang, 2012) (Fig. 1). Moreover, it was also demonstrated that high NAC doses caused increased metastasize, increased ROS production, and increased NRF2 nuclear translocation (Obrador, 2022). NRF2 a is key regulator of expression of molecules performing antioxidant functions in the cell but high NRF2 levels can promote metastasis (Becker, 2023). As was reported, Nrf2 plays a crucial role in the metastasis of cervical cancer by enhancing EMT (Zhang, 2023).

Reports have shown the enhancing effect of NAC on anti-tumor NK cells modified with chimeric antigen receptor (CAR) (Klopotowska, 2022). It was also revealed that NAC also stimulated the antitumor function of exhausted T lymphocytes. The mechanisms of stimulation of NAC action in immune cells are similar to those suggested in cancer cells (Scheffel, 2018).

ANTIANGIOGENIC POTENTIAL OF NAC

It was shown that neoplastic diseases are characterized by high level of pathologic angiogenesis because tumor needs blood supply for growth and development (Radomska-Leśniewska, 2016). As was mentioned above NAC exerted anti-angiogenic properties which were revealed by inhibiting neovascularization both *in vivo* and *in vitro* studies, but also by inhibiting pro-angiogenic markers such as MMP9, Il-8, ICAM-1, and VEGF (Radomska-Leśniewska 2010, Sadowska, 2007, Radomska-Leśniewska, 2006). The mechanism of the antiangiogenic effect of NAC is based on the reduction of the level of HIF-1α by this antioxidant (Gao, 2007). The antiangiogenic activity of NAC promotes the inhibition of tumor growth and development.

Table 1. NAC effect in the study of various types of cancer

Type of cancer in the study	NAC effect	Source
Beneficial effects		
Lung cancer	Enhances EGCG-mediacted cel depletion	Lambert, 2008
Triple-negative breast cancer	Inhibits ROS-mediated signaling – possibly beneficial effect	Kwon, 2021
Breast cancer	Reduces MCT4 and cel proliferation	Monti, 2017
Melanoma	Blocks formation of 8-oxoguanine, reduces oxidative stress – delayed onset of UV-induced melanoma	Cotter, 2007 Goodson, 2009
Glioblastoma	Modulates Notch 2 signaling, prevents cancer proliferation and invasion	Deng, 2019
Lung adenocarcinoma	Suppresses ROS and cancer development	Song, 2018
Pancreatic cancer	Sensitizes to gemcitabine	Qanungo, 2014
Prostate cancer	Prevents growth, adhesion and invasion	Lee, 2011
Tigar/null pancreatic cancer	Inhibits lung metastasis	Cheng, 2023
Melanoma	Stimulates anti-tumor cytotoxic T cells	Scheffel, 2018
Harmful effects		
Lung cancer	Increases metastases	Gill, 2016 Breau, 2019 Wiel, 2019
Lung cancer	With vitamin E increases proliferation, reduces ROS and p53 levels.	Sayin, 2014
Melanoma	Increases proliferation and migration.	Piskounova, 2015 Le Gal, 2015
Melanoma	Increases metastases and Nrf2 nuclear translocation	Obrador, 2022
Breast cancer	Reduces ROS levels, increases expression of metastasis-related genes	Liang, 2012

ECGG – epigallocatechin-3-gallate MCT4 – monocarboxylate transporter 4

PREVENTIVE POTENTIAL OF NAC

It is suggested that NAC and other antioxidants may potentially prevent cancer, because DNA damage caused by oxidative stress and genome instability may lead to cancerous transformation (Radomska-Leśniewska, 2016). A clinical trial in which patients were given 1,800 mg of NAC daily showed that this

was a sufficient dose to prevent cancer and lower markers of oxidative stress (Block, 2008). The "Euro-scan" study, in which only 600 mg of NAC was administered daily, did not show positive results in patients with head, neck and lung cancer, probably due to too low dose of the drug (van Zandwijk, 2000). Then preventive capabilities of NAC can be dose-depended. Many other studies on the prevention and anticancer and antiangiogenic effects of NAC have been performed *in vitro* and in animal models. These studies demonstrated the effectiveness of NAC in cancer prevention (De Flora, 1996; Reliene, 2006). NAC administered in drinking water inhibited the incidence and proliferation of tumors in lymphoma-bearing mice with the ataxia telangiectasia mutation (Reliene, 2006). Moreover, inhibition of metastasis and cell proliferation has been described in a tumor angiogenesis model in athymic breast cancer-bearing mice treated by NAC (Agarwal, 2004). NAC was shown to be a potential pharmacological agent for the prevention and treatment of cervical cancer. In this study, NAC promoted apoptosis in HPV-positive cells and effectively reduced the proliferation of HPV-positive cells by inhibiting cIAP2 and HIF-1α (Guo, 2023).

Gao et al. found that NAC (applied in drinking water) inhibited three *in vivo* mouse tumor models. The NAC effect was mediated by inhibition of HIF-1 levels in a MYC-dependent human B lymphoma model (Gao, 2007). A similar anticancer/antiangiogenic NAC effect was obtained in multiple studies performed on cell lines including human melanoma (Cotter, 2007), lung cancer cells (H1299) (Liu, 2012), androgen-independent prostate carcinoma PC-3 cells (Lee 2011), and others (Tab. 1).

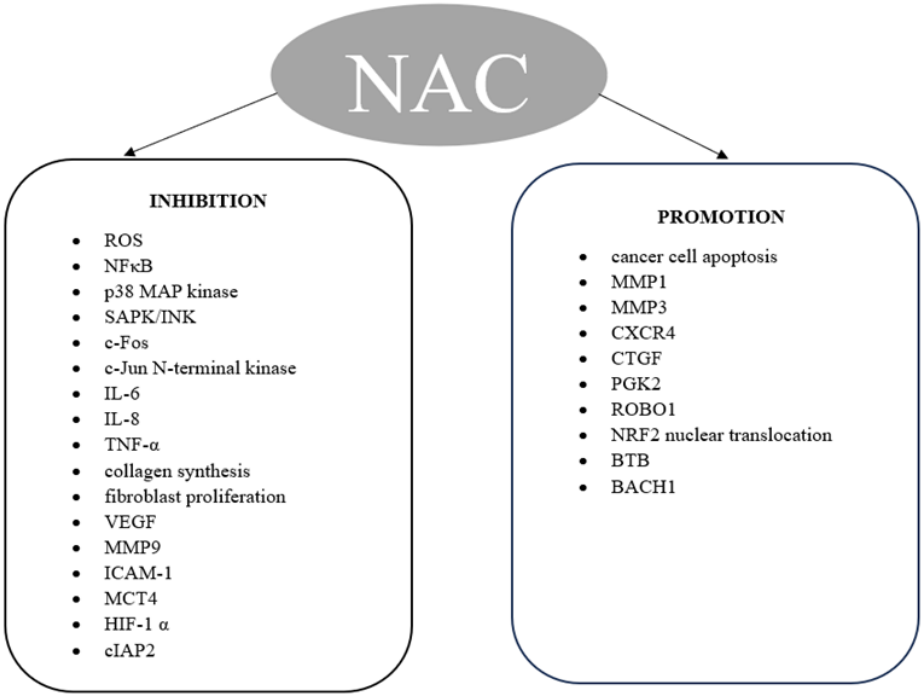

Figure 1. The Effect of NAC on molecular pathways components and molecules levels

RADIO- AND CHEMOPREVENTIVE ACTIVITY OF NAC

Although radiotherapy (RT) and chemotherapy is an important components of cancer treatment, they induces adverse tissue reactions in the around of cancer tissue. Therefore, radioprotective agent is needed to secure normal tissues.

Barlaz et al. reported a radioprotective effect of NAC on RT-induced cardiac damage in rats for the acute term. Results supporting cardiac injury were observed in the electrocardiogram. Furthermore, cytokine levels and oxidative stress were also significantly increased. NAC was reported to reduce these signs of cardiac damage and, therefore may be a potential radioprotector that is capable of preventing cardiac damage (Barlaz, 2020).

NAC administered at a dose of 2,400 mg by nebulization for 8 weeks to patients after radiotherapy with head and neck cancer improved their quality of life expressed by a greater reduction in the use of analgesic drugs and improved xerostomia (Won, 2020). Similar results (improved xerostomia and saliva thickening) were obtained in a study of patients with head and neck cancer who had rinsed their mouths with NAC

(2,500 mg daily) before and after radiotherapy (Sio, 2019). Moreover, in patients with the same cancer, transtympanic NAC injections performed before radiotherapy prevented cisplatin-induced ototoxicity (Yoo, 2014).

A meta-analysis study revealed that NAC and other antioxidants inhibit the toxicity caused by cancer therapy in most cases (Block, 2008). In a group of 40 children with acute lymphoblastic leukemia after chemotherapy/radiotherapy, vitamin E and NAC were proven to be effective as adjuvant antioxidant therapy. The toxicity of chemotherapy and radiotherapy was significantly reduced as measured by reduced levels of malondialdehyde, increased levels of glutathione peroxidase, and reduced incidence of toxic hepatitis (Al-Tonbary, 2009).

SUMMARY AND CONCLUSION

NAC supplementation can reduce tumor cell proliferation, migration, and invasion in various types of cancer. It also has chemopreventive properties, eliminating the negative effects of chemotherapy and radiotherapy. The preventive effect of NAC is also known. However, caution should be exercised when using NAC in cancer patients, especially with regard to metastases, as NAC was reported to intensify them in some studies. Thus, results of using of NAC in humans, may depend on stage of cancer as well as tumor type and organ subject to colonization. Moreover, the reason for the various effects of NAC in cancer treatment seems to be the involvement of this drug in the modulation of signaling pathways that can induce or inhibit cancer. Further research is needed to resolve the role of NAC in cancer treatment.

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