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Secondary Metabolites from *Saccharomyces cerevisiae* Species with Anticancer Potential

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Abstract

Chemotherapeutic agents produce from numerous sources such as animals, plants and micro-organisms are derived from the natural products. Although the existing therapeutic pipeline lacks fungal-derived metabolites, but hundreds of secondary metabolites derived from fungi are known to be possible chemotherapies. Over the past three decades, several secondary metabolites such as flavonoids, alkaloids, phenolic and polyketides have been developed by *Saccharomyces cerevisiae* species with exciting activities that considered valued for the growth of new chemotherapeutic agents. Many secondary metabolites are protective compounds which prevent abiotic and biotic stresses, i.e. predation, infection, drought and ultraviolet. Though not taking part in a living cell's central metabolism, secondary metabolites play an important role in the function of an organism. Nevertheless, due to slow biomass build-up and inadequate synthesis by the natural host the yield of secondary metabolites is low by direct isolation. A detailed comprehension of biosynthetic pathways for development of secondary metabolites are necessary for *S. cerevisiae* biotransformation. These metabolites have higher inhibitory effect, specificity among cancer and normal cells, and the mechanism of non-apoptotic cell killing. This study shows the significance of bioactive compounds produced by *S. cerevisiae* species with their possible activity and value in chemotherapeutic drugs pipeline. The isolation and alteration of these natural secondary metabolites would promote the development of chemotherapeutic drugs.

Keywords: *Saccharomyces cerevisiae*, secondary metabolites, anticancer activity, synthetic biology, bioactive compounds

1. Introduction

Yeast is a single-celled eukaryotic microorganism that belongs to the kingdom of fungi. About 1500 yeast species have been correctly described since the discovery of the first yeast [1]. Yet 1% of all known fungal members are stated to be yeast species. *Saccharomyces cerevisiae*, budding yeas, also represents a typical industrial microorganism used in basic molecular biology research as a main model organism and was the first eukaryotic organism to have completely sequenced its genome.

A single-cell fungus, *Saccharomyces cerevisiae*, is also known as a Baker's yeast [2]. *Saccharomyces cerevisiae* is the eukaryotic microorganism most extensively studied, which allows us to understand the eukaryotic cell biology and subsequently the physiology of human. For several hundred years, in food processing and alcoholic drinks, *S. cerevisiae* have been used, and this organism is still used today in a variety of different pharmaceutical processes. It functions very well as it is non-pathogenic and is classified by GRAS organism (generally regarded as safe) due to the long history of use in the development of consumables such as ethanol and baker's yeast [3].

The sum of all organismic biochemical reactions can be described as metabolism. Metabolites are the products and intermediates of metabolism and are generally limited to small molecules. Natural products come from a variety of sources, including animal species, land-based plants, aquatic organisms, land invertebrates and vertebrates, microorganisms as secondary metabolite products [4]. The word "secondary" proposed by A. Kossel in 1891 means that while in any living cell primary metabolites are present, the secondary metabolites are only present at a by-product and are of no significant importance to the life of the organism. Although the primary metabolism derives secondary metabolites, these secondary metabolites do not constitute the organism's fundamental molecular framework. Although the secondary metabolites do not participate in central metabolic processes of a living cell, they play an important role in the function of an organism. Many secondary bioactive compounds defend against biotic and abiotic and biotic stresses including predation, cancer, drought and ultraviolet radiations. Its absence does not reduce the life of an organism, which is a feature contrary to primary metabolite, instantly, but largely affected the organism's survival. Currently there are a range of analytical platforms for metabolomics research, among which are including mass spectrometry direct infusion (MS), gas chromatography linked to mass spectrometry (GC-MS), gas chromatography linking to mass spectrometry two-dimensional (GC, GC-MS), liquid chromatography coupled to mass spectrometry (LC-MS), capillary electrophoresis to mass spectrometry coupling (CE-MS), and proton nuclear magnetic resonance spectroscopy (^1H NMR) [5].

These complex structural and chemical molecules serve as an excellent therapeutic class to cure many diseases. Around 80 percent of all drugs were derived from plant sources at the beginning of 1900. Alexander Fleming's discovery of penicillin from *Penicillium notatum* in 1928 marked a major change as a source of natural product from plants to micro-organisms. In medicine, agriculture, food industry and scientific research microorganism-derived compounds since then have been used [6]. But, due to the slow accumulation by biomass and inadequate synthesis by the host, the production of secondary metabolites by direct isolation is poor. Exhaustive awareness of biosynthetic pathways for the production of secondary metabolites are necessary for the development of *S. cerevisiae* biotransformation. Progress in synthetic biology has made it possible to develop a number of bioinformatics tools that can be utilized to create new regulatory elements and secondary metabolite synthesis pathways [7].

Because of its similar metabolism *Saccharomyces cerevisiae* was used as a biologically similar model for higher eukaryote organisms. The expression of heterogeneous pathways is less difficult relative to other kinds because of its eukaryotic nature. For example, prokaryotes do not conduct any post-translational modifications, and protein miss-folding and membrane translation can be an annoyance [8]. During preclinical or clinical testing, a well-characterized yeast metabolite, such as flavonoids, alkaloids, phenolic and polyketides, exhibit remarkable anti-tumor properties unexpectedly. Although its basic action mechanism is still being studied, evidence shows that its actions are operationally directed toward core regulatory pathways and dysregulated enzymes during cancer pathogenesis.

Since ancient time, from the days of the Pharaohs in ancient Egypt, cancer continues to plague humanity. It derives its name from Hippocrates, father of medicine, who had been using the Greek-named “Karkinos” to talk about tumors, nevertheless these earliest view about this infection are different from modern concept. Cancer has been characterized as an irregular growth in cells caused by several changes in gene-expression leading to dysregulated equilibrium between death of cell and proliferation eventually developing into cell populations that can invade and metastasize tissues in distant sites and cause severe host death if left unsanctioned according to the World Health Organization (WHO). About 60 percent of all anticancer medications currently available in clinics are natural or derived from natural product modification substances. In the 1950s interest in the discovery and production of vinblastine, vinka alkaloids and vincristine, and later taxol from Pacific yew bark, *Taxus brevifolia*, in the pursuit of natural anticancer agents began earnestly. Then, our awareness of the metabolites of *S. cerevisiae* have also been further progressed in cancer therapy and have reported antitumor action against the overwhelming majority of cancers, like lymphoma, leukemia and solid tumors. Far from the suppression of tumor development, the delay of tumor progression, and an effect on tumor-cell metastatic and invading therapy, these metabolite combinations have almost all demonstrated strong therapeutic benefit at the preclinical level. Some of these allegedly promising metabolite compounds are discussed individually below [9].

2. Production of secondary metabolites via *S. cerevisiae*

Apart from essential metabolites (carbons, proteins, amino acids, vitamins, acetones, ethanol, etc.), *S. cerevisiae* offers a wide range of secondary metabolites during active cell development, including toxins, antibiotics, fatty acids, alkaloids, alcohols, ketones etc. Secondary metabolites (SM's), which are not necessary for organism growth, are classified as diverse low molecular-weighted compounds. For a number of purposes, *S. cerevisiae* use secondary metabolites such as stress prevention, predation defense, competitiveness, communications, pathogenicity and exposure of other organisms. A small number of primary metabolism precursor metabolites are used to biosynthesize secondary metabolites [10].

A number of bioactive compounds, including terpenoids, polyketides, alkaloids and non-ribosomal peptides can be produced in *Saccharomyces cerevisiae* (Figure 1). Such precursors are mainly short chain carboxylic acids (for example, acetyl-coA) or amino acids in *Saccharomyces cerevisiae* species which are connected to synthesized polyketides by backbone enzymes such as polyketide synthases (PKSs). Terpenoids production is catalyzed by terpene cyclase and production starting from dimethyl allyl diphosphate derived from (or isoprene). Non-ribosomal peptide synthetases (NRPSs) using modified and natural amino acids to synthesize non-ribosomal peptides. Diverse enzymes are used to catalyze the synthesis of alkaloids from amino acid. These secondary metabolites can naturally be synthesized as industrial products, particularly pharmaceutical products, from host (native) cells.

Many other reports have shown that the genes involved in biosynthetic secondary metabolites are known as biosynthetic gene clusters (BGCs). This have been shown that genes that encode significant biosynthesis (for example; polyketides synthase) are supplementary enzymes and precursors in the pathways of biosynthesis. Consequently, all significant genes are discovered in the BGCs that participate in the synthesis of bioactive compounds [11, 12]. The production and complementary regulation of catalytic properties can produce incredibly useful secondary metabolites for these biochemical transformations BGC enzymes [13].

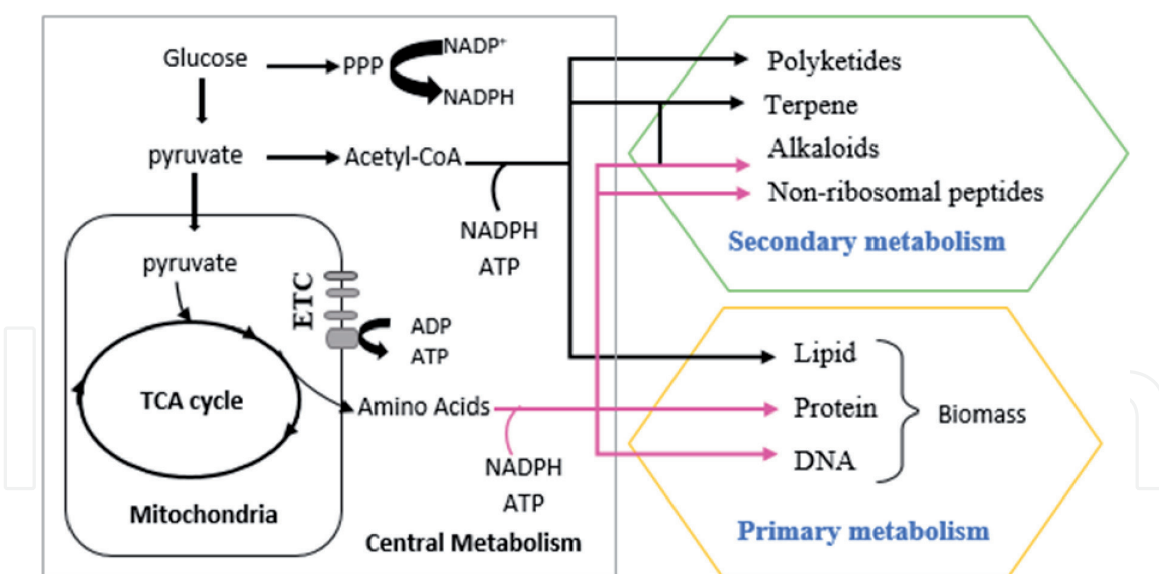


Figure 1.

A short description of the formation pathways of secondary metabolites [11, 12]. Four sub-groups of microorganism and plant-generative metabolites involve terpenoids, polyketides, non-ribosomal peptides and alkaloids. Biosynthetic genes (BGC's) are structurally classified into the genes that encrypt major biosynthetic enzymes, supplementary enzymes, precursors in the process of biosynthesizing, resistance factors or transporters in secondary metabolite formation.

The methods and technology used to improve pharmaceutical production of secondary metabolites in the *S. cerevisiae* have advanced rapidly in recent years.

We discuss below the progress in developing biosynthetic pathways of *Saccharomyces cerevisiae*' secondary metabolites with anticancer potential: alkaloids, phenolic, terpenoids, polyketides, non-ribosomal peptides, and vitamin C.

3. Alkaloids

Several studies have used *S. cerevisiae* in recent years as a host to engineer the biosynthetic process of alkaloids. Alkaloids are complex nitrogen molecules that are extremely bioactive. There are reportedly approximately 50 alkaloid medications, including vincristine (cancer drug), codeine (analgesic drug) and noscapine (anti-tussive drug). They are unique for the cell cycle and the process, because they block metaphase (M phase) in mitosis. They block tubulin's ability to form microtubules via polymerization. Dysfunctional spindle structures, avoid chromosome separation and cell proliferation. Strictosidine, which had been synthesized by novo, was the earliest study of alkaloid plant origin in *Saccharomyces cerevisiae* strains [14]. Strictosidine is a significant intermediate product in the terpenoids Indole alkaloids (TIAs) biosynthesis that include vincristine (antitumor) and ajmalicine (anti-hypertensive) [15].

The metabolic course of *Saccharomyces cerevisiae* for protoberberine alkaloid (S) canadine from racnorlaudanolin has been optimized by Galanie et al. [16]. The secondary metabolite of Berberine has numerous pharmacological effects, such as antidiabetics, antibacterial, anti-ulcerones and anti-inflammatory effects. In vivo and vitro experiments with berberine, the results of arresting cell cycle during G1 or G2/M and apoptosis of tumor cell were shown to be anti-cancer activity. Berberine also was found to induce autophagy and stress in the endoplasmic reticulum, resulting in the invasion and inhibition of the tumor cells. Berberine has been proven to lower angiogenesis by decreasing expression of VEGF in addition to its apoptotic effects. The cancer cell migration was also decreased. In the respective

complexes, Berberine attaches to DNA or RNA. Berberine also stimulates P53, which contributes to cell cycle arrest and apoptosis. Berberine has been shown to induce apoptosis as well via DNA interactions and pathways that are dependent on mitochondrial [17].

4. Phenolic

Phenolic are a large category of secondary plant metabolites that have at least one hydroxylated ring. Flavonoids and stilbenes are two groups of metabolites highly appreciated as a nutrient and therapeutic agent among the phenolic developed by phenylpropanoid pathways in the plant [18]. As a host cell, *Saccharomyces cerevisiae* is well equipped to promote phenolic compound biosynthesis. The following phases include cancer development: initiation, development, proliferation, invasion and metastasis. Initiation links by free radicals, inflammatory mediators, radiation, smoke of cigarette that damage the DNA-product, which can cause genetic mutation and replication of cells which are mutated results to cause carcinogenesis [19].

It has been noted that phenolic compounds i.e. ellagic acid and delphinidin show significant protective effects for example, apoptotic activity in colon cancer cells. In prostate, liver and leukemia cancer cells, delphinidin also showed significant activity. Cell apoptosis can also be caused by phenolic compounds. The mechanisms of invasion and migration of human cancer are also updated (Figure 2) [20].

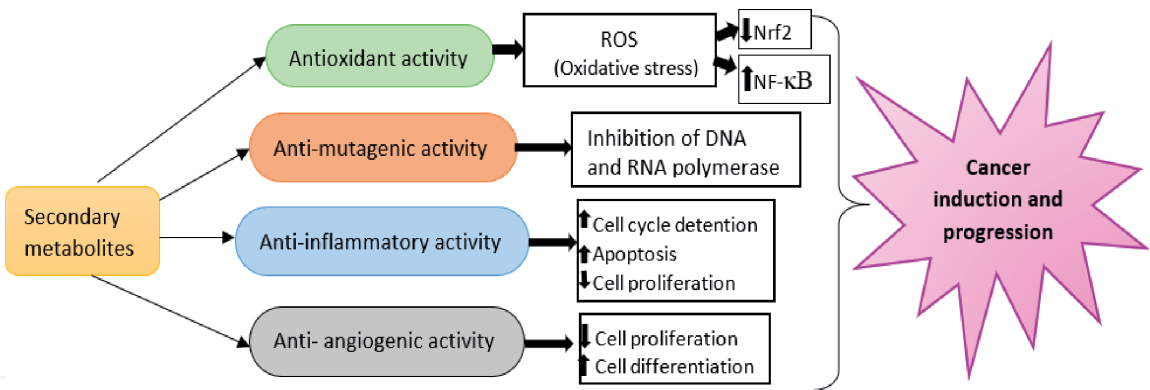


Figure 2.
Potential of secondary metabolite protective mechanisms for cancer management [17].

5. Flavonoids

The *Saccharomyces cerevisiae* strains have been developed by researchers, which synthesize various flavonoids, from the main phenolic intermediates to flavones, flavanones, flavonols and isoflavones. Phenylalanine is transformed into p-coumaric acid, a common phenylpropanoid precursor, in two sequence reactions in the initial steps of the phenylpropanoid pathway. *S. cerevisiae* is an ideal flavonoid host strain. One of the first studies on *S. cerevisiae* for flavonoid production was carried out according to [21]. The first flavonoid analysis was published on the synthesis of naringenin, major intermediate of flavonoid, from glucose in engineered *Saccharomyces cerevisiae* [22]. In *Saccharomyces cerevisiae* p-coumaric acid was used as a precursor for other flavonoids including apigenin, chrysin and luteolin. Anti-inflammatory, cardio-protective and anticancer effects were observed for quercetin, kaempferol, and fisetin [23].

More flavonoid intake has been reported to reduce cancer risk. In this respect, there have been reports of a variety of mechanisms including arresting of cell cycle, proliferation inhibition, apoptosis induction, anti-oxidation etc. These flavonoid extracts' cytotoxic activity makes them capable to produce cancer drugs. Flavonoids from *Saccharomyces cerevisiae* have potential to treat cancer treatment at all stages is therefore important for the recognition of harmless constituents against cancer as important for chemotherapy. Therefore, for producing cancer medicines, it is important to distinguish effective components from the yeast strain. Flavonoid-treated HeLa cells displayed apoptosis and loss of mitochondrial membrane potential (MMP). The toxic effect of flavonoid extracts makes them attractive candidates for cancer drug development. Such treatments have been found to inhibit growth across many lines of cancer cell, including cancer of the colon, breast cancer, carcinoma of squamous cell and hepatocellular carcinoma etc. Another study concerning bioactive flavonol "fisetin" found that fistein treatment caused cell viability by regulating the arresting G1 phase of human in melanoma cells [24].

6. Terpenoids

Many terpenoids were developed by engineering the related metabolic pathways in *Saccharomyces cerevisiae*. The first study about the medically useful development of terpenoids in yeast was the amorphaadiene synthesis in *Saccharomyces cerevisiae*. The sigma ling of NF- κ B, the key regulator in pathogenesis for cancer and inflammation, can be inhibited by natural terpenoids. Various mechanisms, such as the induction of apoptosis, have been found in terpenoid cancer. The natural terpenoids are quite well identified as NF- κ B signaling inhibitors. Yeast also produces taxol (class of di-terpenoid), which is a common cancer medicine [25]. *Saccharomyces cerevisiae* has been metabolically adapted for the synthesis of taxa diene as a primary trial for taxol synthesis in a microbial host [26]. Paclitaxel (generally called taxol) is a common and strong drug used in chemotherapy for cancer. Taxol has the anti-tumor property due to its attachment to microtubule protein i.e. β -tubulin. As a result, the micro tubular dynamics have been suppressed and acetylation of α -tubulin protein has been increased. Mitosis can be prevented by increase in micro tubular and thus contributes to the cell's death.

The carotenoids were the first kind of isoprenoids formed in the *Saccharomyces cerevisiae*. These compounds are found to cardiovascular and osteoporosis anti-oxidant with therapeutic effects and to have anticancer activity by the activation of the NF- κ B signaling pathway. LPS are reduced by signaling caused by β -carotene. It also reduces the I κ B protein and prevents p65 subunit nuclear translocation and also prevent the NF- κ B complex binding with DNA. β -carotene prevents cancer progression by virtue of its proxidant function [27].

7. Polyketides

Polyketides form a large group of bioactive compounds, which vary in pharmacology and structure, and cover different drugs like antibiotics and antitumor. The polyketides are synthesized by large enzymes called polyketide (PKS) as secondary metabolites in particular by fungi and bacteria. The Synthesis of dihydrochalcones (DHCs) is an example of the polyketide development of metabolic *Saccharomyces cerevisiae* strain. One polyketide derivative with antidiabetic and antioxidant activity is DHCs such as nothofagin and phlorizin. Preclinical trials indicate that its

primary effect is to disrupt the dynamics of microtubule by reducing micro tubular polymerization and contribute to apoptosis. However, the mechanisms used to regulate eribulin's action were not fully elucidated [28]. Other pre-clinical studies in eribulin have demonstrated its ability in breast and colon cancer to suppress tumor growth in xenograft models of mouse. In metastatic breast cancer trials, clinical studies have shown that this compound is viable. Additional phase III analysis showed that eribulin as though only other two therapeutic drugs (taxane and anthracyclines) increases overall survival in pre-treated patients with severe breast cancer (**Figure 3**) [29].

Activation of the caspase is conducted along two separate routes: the cell membrane mediated pathway of the death recipient and the mitochondrial pathways. Rising Bax protein levels with a related decrease in the Bcl-2 protein have been shown by the two studies. A rise in the Bax/Bcl-2 ratio is well known to encourage cytochrome c release from mitochondria into the cytosol, culminating in the triggering of caspase-3, which is a cause for apoptosis initiation. A variety of signal transduction pathways and regulatory pathways contribute, among other things, to the upregulation of apoptosis genes are recorded to involve protein–protein interactions (PPIs) and their associated protein [30]. STAT-3 seem to have an effect on the migration of the tumor and glioblastoma cells, non-small cell lung cancer (NSCLC), renal system of human which have shown a metabolite disturb this

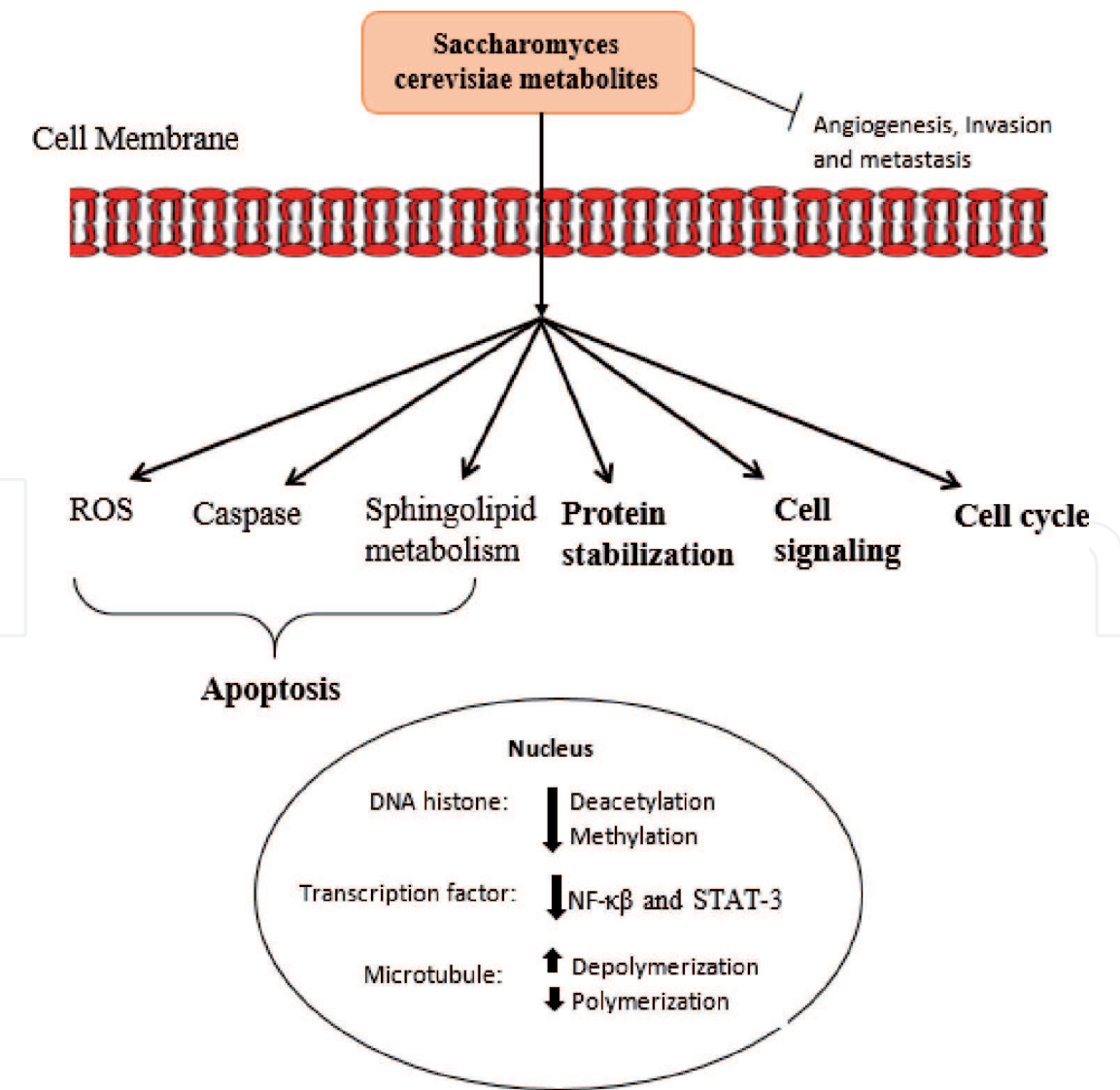


Figure 3.
Targets of Saccharomyces cerevisiae secondary metabolites in tumor cells [9].

system which indicates that the mechanism is likely to slow or suppress solid tumors in the metastatic process [31].

8. Non-ribosomal peptides (NRPSs)

Gurma is a 35-residue peptide widely used as a medical product in sweet-tasting transduction studies because of its ability to specifically inhibit neural responses for sweet matter in rats and mice is an example of the non-ribosomal peptide synthesis in modified yeast. Early research has shown that NRPSs are involved in the development of some of our key antiviral, anticancer, antibacterial and immunosuppressant medicines even though they are not progenitors of this ribosome. It has been determined the bleomycins are a group of glycosylated peptides which Umezawa and his colleagues found to be active against cancer in the 1960s. Bleomycin A2 and B2 is a major component of the clinical medicine, bleomycin. Carcinoma of cell squamous, lymphomas, esophageal cancer, testicular cancer and recalcitrant warts have been treated with bleomycin. This iron-bleomycin complex, mostly ferrous ions which interacts with oxygen and creates reactive free radical. Specifically, the free radicals respond to the abstraction of DNA deoxyribose hydrogen from C4' and lead to one or two-strand breaks, mainly of G-T and G-C at pyrimidines [32].

Several compounds for the production of novel anticancer drugs have recently come into being. However, the pathways involved in the cytotoxicity of these compounds in tumor cell lines are still widely ignored but many studies point to a significance in apoptosis. For example, a number of compounds impeding cell growth in a wide range of cell lines of cancer have been shown to be still poorly elucidated by which cancer cells are hampered. Compounds were identified in some cases to cause cell death by the triggering of the apoptotic pathway; however, more studies were required in the mechanisms involved apoptosis. Some compounds created an imbalance in the ability of the cell redox, with mitochondria playing a key role in this phase. Further studies are required to explain this, however. A further impaired process is cell cycle, primarily as a result of actin and micro tubular filament interruption, yet only a few studies are conducted to link marine NRPs with cell cycle alterations, and further research are necessary to clarify their intervention in the process [33].

9. Vitamin C

L-ascorbic acid (Vitamin C and L-AA or) is a water-soluble effective antioxidant used as a ROS scavenger to defend against or at least reduce the harmful effects caused by ROS in most eukaryotic species. ROS is a common source of various types of cancer and considered vitamin C have a beneficial impact on reductions of lung, colorectal and stomach cancer [34]. On the other hand, vitamin C can, under some circumstances, enhance the production of ROS and may have adverse effects under some circumstances [35].

However, the ability of yeast cells to generate L-AA is normal. Erythro-ascorbic acid is instead present at a low concentration in yeast cells as a structurally connected substance with chemical composition identical to L-AA. The vitamin C biosynthesis from D-glucose in *S. cerevisiae* cells that was recombinant by using a plant paths is first recorded according to [36]. In two distinct strains, ascorbic acid accumulation was shown to be effective, and the effect from a distinct genetic context was studied in parallel [37].

10. Future perspectives

Further studies on the kinds of chemical components and the purification of different bioactive groupings could show the full capacity for certain pathogenic microbes inhibited by the *Saccharomyces cerevisiae* extract. The creation of a catalog of *Saccharomyces cerevisiae* processing hosts which are produced for the supply by the overproduction of central metabolites of sufficient precursors for heterologous pathways introduced can be aimed at future efforts in the sector. These modified strains often have the effect of modifying the functioning of organelle and cell membrane processes in order to enable the efficient use of substrates, product exports, intermediate retention and partitioning.

Additional crucial components are the compatibility between the introduced foreign secondary metabolite genes and the *Saccharomyces cerevisiae* host, including highly enhanced host pathway expression, metabolic stress/contamination, sufficient resistance/export of secondary metabolites etc. The strengthening of the hierarchical regulatory waterfalls within the host cell and the incorporation of appropriate promoters into the inserted BGC could help to improve the BGC expression for the secondary bioactive metabolite of an engineered host. Then, the resistant and exporting genes derived from or from original biosynthetic gene clusters or selected from other clusters of genes, other secondary source metabolites or even environment metagenomes might reduce the toxicity and metabolic burden on the host cell due to synthesis of secondary metabolites. In the coming years activities in other yeast species will be further investigated in order to identify additional results and obtain more high-performance products in this area instead of *Saccharomyces cerevisiae* in pharmaceutical secondary metabolites.

11. Conclusion

In summing up this paper, remarkable developments in the field of yeast cell and molecular biology have taken place in the last two decades, especially as cell engineering, genome sequencing and synthetic technology have grown rapidly. Many useful pharmaceuticals and metabolites were developed using modified *Saccharomyces cerevisiae*. These results support a strong prediction that secondary metabolites from *Saccharomyces cerevisiae* can be perceived to occur as single pharmacological compounds. The metabolites also target key regulatory pathways in cancer cells, normal cells and tissues. Until human trials are launched on cancer subjects, fungal metabolites must, however, undergo stringent quality control and pharmacological dose-scaling evaluations. In addition, high-end screening methods need to be standardized because new metabolites are constantly identified for the yeast metabolite library survey. Isolating and altering these secondary metabolites would enable the development of chemotherapy drugs.

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