Journal of American Science

Websites:
http://www.jofamericanscience.org
http://www.sciencepub.net

Emails:
editor@sciencepub.net
sciencepub@gmail.com

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Microbial source of L-methioninase as anticancer agent

Bali MH

University of Jeddah, KSA

Abstract: This dealt with various aspects of chemotherapy such as (a) problems connected with the design of new and more effective agents with selective enzyme inhibition on given tissues; the biochemical differences between responsive and nonresponsive tumours particularly in regard to their metabolism of a given drug; (c) the necessity of more biochemical and pharmacology knowledge on which to base schedules of drug administration; (d) the necessity of individualizing clinical treatment as shown by data on drug metabolism; and (e) discussion of what has been accomplished toward curing certain forms of cancer with chemotherapy.
[Bali MH. **Microbial source of L-methioninase as anticancer agent.** *J Am Sci* 2020;16(4):73-80]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 6. doi:10.7537/marsjas160420.06.

Keywords: Microbial; source; L-methioninase; anticancer; agent

Overview of cancer:

The normal cell turns into a cancer cell because of one or more mutations in its DNA, which can be acquired or inherited as discussed by (Haber and Fearon, 1998). However, carcinogenesis is a complex multistage process, usually involving more than one genetic change as well as other epigenetic factors (hormonal, carcinogenic and tumour-promoter effects) that do not themselves produce cancer, but increase the likelihood of the genetic mutations resulting eventually in cancer (Sundar, 2014).

The cancer cells proliferate abnormally. Therefore, they required a high amount of amino acids as nutrients because they are the building blocks for protein synthesis. So without amino acid, tumour cells fail to function because proteins cannot be synthesized. According to this concept recent research has targeted on amino acid metabolic enzymes that deregulate specific amino acid metabolism that is essential for cancer cell proliferation (Supriya and Prajapati, 2018).

Cancer-chemotherapy:

Chemotherapy is the use of strong drugs to kill cancer cells. It is often called (chemo) if the disease has spread in the body, or it is likely to spread; Chemotherapy drugs are used there are many types of chemotherapy, depending on the types of cancer, the stage and the patients (Diane and Elisabeth, 2019). To date, cancer remains one of the most life-threatening diseases. Even today the mortality rate or survival time for metastatic cancer has not been prolonged as reported by (Chong *et al.*, 2006). Some tumours require the extracellular sources of some amino acids, which are considered as non-essential in normal cells, due to metabolic deficiencies (Kuo *et al.*, 2010). Enzymatic degradation of these amino acids can be an effective strategy in the suppression of such tumours (Shen *et al.*, 2006).

This dealt with various aspects of chemotherapy such as (a) problems connected with the design of new and more effective agents with selective enzyme inhibition on given tissues; the biochemical differences between responsive and nonresponsive tumour particularly in regard to their metabolism of a given drug; (c) the necessity of more biochemical and pharmacology knowledge on which to base schedules of drug administration; (d) the necessity of individualizing clinical treatment as shown by data on drug metabolism; and (e) discussion of what has been accomplished toward curing certain forms of cancer with chemotherapy (e.g., trophoblastic and testicular cancers, certain lymphomas), and what the future prospects are for increasing the number of chemotherapeutic cures.

Role of microbial enzymes in cancer therapy:

Enzymes are biological catalysts (biocatalysts) that enhance the biochemical reactions in living organisms. They can also be extracted from cells and used to catalyze a range of commercially essential processes (Robinson, 2015).

Enzymes which function as drugs differ from all other types of drugs by two main features. First, proteins are known by their affinity and specificity when they act on their targets. Second, they catalyze and convert multiple target molecules to the desired products. These two features make enzymes specific and potent drugs that can accomplish therapeutic biochemistry in the body that small molecules cannot. These characteristics have resulted in the development of enzyme drugs for many diseases (Sundar, 2014).

Therapeutic enzymes (digestive and metabolic) are applied medically either isolated or adjunct with other therapies to cure diseases like cancer, cystic fibrosis, dermal ulcers, inflammation, gastrointestinal disorders, etc. Enzymes as direct pharmaceutical products have numerous applications, including their uses as antitumour (Kaur and Sekhon, 2012).

Enzyme therapies are becoming more prevalent in medicine today, with many manufacturers targeting their advantages in disease treatment. Enzymes have two significant features that differentiate them from all other types of drugs. First, enzymes frequently bind and act on their targeted sites with high affinity and specificity. Second, enzymes are catalytic and convert numerous target molecules to the desired products. These two important features make enzymes specific and potent drugs that can achieve therapeutic biochemistry in the body that small molecules cannot. These features have resulted in the development of many enzyme-based drugs for a wide range of disorders (Vellard, 2003).

Research on cancer provides examples of the use of therapeutics enzyme (Sundar, 2014). Some tumours require the extracellular sources of some amino acids, which are considered as non-essential in normal cells, due to the metabolic lack (Stone et al., 2010; Kuo et al., 2010). Thus, when the enzymatic degradation happens on these amino acids, tumours can be suppressed (Shen et al., 2006). The enzymes treatment of cancer has a long history, first in 1902 with the work of Dr John Beard, professor at the University of Edinburgh proposed that the pancreatic proteolytic enzyme trypsin represent a powerful anti-cancer tool. Later, there are several enzymes are used for cancer treatment like methionine syntheses (Kenyon, 2002); Pyridoxal 5-Phosphate (PLP) dependent enzymes (Percudani and Peracchi, 2003); L-methioninase (El Sayed and Shindia, 2011); and L-arginase, L-tyrosinase, a-, B-glucosidase and B-galactosidase (Kaur and Sekhon, 2012). The antitumour enzymes in particular can affect the metabolic pathways of tumour cells and promote apop tosis since the malignant cells generally cannot repair themselves effectively (Elisabetta et al., 2008).

Enzymes have two significant features that differentiate them from all other types of drugs. First, enzymes frequently bind and act on their targeted sites with high affinity and specificity. Second, enzymes are catalytic and convert numerous target molecules to the desired products. These two important features make enzymes specific and potent drugs that can achieve therapeutic biochemistry in the body that small molecules cannot. These features have resulted in the development of many enzyme-based drugs for a wide range of disorders (Vellard, 3003).

In traditional medicine, proteolytic enzymes derived from plant extracts have been used for a long time In addition to proteolytic enzymes from natural resources such as plants, ‘modern’ enzyme therapy includes pancreatic enzymes. Therapeutically, the use of proteolytic enzymes is partly based on scientific reports and is partly empirical [Gurung et al., 2013 43]. Clinical evidence of the use of proteolytic enzymes in cancer studies has typically been obtained with an enzyme preparation comprising a combination of papain, trypsin and chymotrypsin. Earlier reports proved that enzyme therapy can reduce the adverse effects caused by radiotherapy and chemotherapy. There is also a report available that, in some types of tumours, survival may be sustained. The positive effects of systemic enzyme therapy appear to be based on its anti-inflammatory potential. Nevertheless, the exact mechanism of action of systemic enzyme therapy remains unsolved. The proportion of proteinases to anti-proteinases, which is regularly used as a prognostic marker in cancer studies, is likely to be influenced by the oral administration of proteolytic enzymes, most likely via induction of the synthesis of anti-proteinases. In addition, there are many alterations of cytokine composition during treatment with orally administered enzymes, which might be a sing of the efficacy of enzyme therapy (Leiper and Saller, 2ooo)

In the treatment of cancer, many enzymes were used, such as arginine-degrading enzymes consist of three main types of proteins: arginine deiminase, arginase and arginine decarboxylase which exist in archaea, bacteria, and eukarya (Zúñiga et al., 2002; Knodler et al., 1998). L-asparginase is a therapeutic enzyme found in bacteria, fungi, yeast, actinomycetes, algae and plants, and It has gained importance due to its potential effect as an anti-cancer agent against tumour cells (Unissa et al., 2015).

L-glutaminase activity is widely distributed in an animal, plant tissues and microorganisms including bacteria, fungi, and actinomycetes. Microbial L-glutaminase has received greater attention for its potential biotechnological applications and easiness in large-scale production (Binod et al., 2017). The L-glutaminase has also shown good radical scavenging activity which could have used in the medical field, like anti-tumour agent (More et al., 2016). ASNase is the example of amino acid depriving enzymes, which has been applied in the treatment of acute lymphoblastic leukaemia for many years (Piatkowska-Jakubas et al., 2008). L-methioninase as a pyridoxal 5'-phosphate-dependent multifunctional enzyme (Takakura et al., 2004). The activity of L-methioninase was extensively documented against several types of cancers including breast, kidney, colon, lung, and prostate cell lines (Tan et al., 1996).

L-methioninase is ubiquitous in almost of organisms, including bacteria, fungi, protozoa, and plants, except mammals (El-Sayed, 2010)

Microbial enzymes are preferred over plant or animal sources due to their economic production, ease of process modification and optimization of its production, more stable than corresponding enzymes derived from plants or animals. They provide a greater diversity of catalytic activities. The majority enzymes currently were used in industry are of microbial origin, and the vast majority of these are produced from only about 25 species, including 12 species of fungi (Kaur and Sekhon, 2012).

L-Methioninase:

This enzyme belongs to the family of lyases, especially the class of Carbon-sulfur layers, the systematic name of this enzyme class is L-methionine methanethiol-lyase (deaminating 2-oxobutanoate-forming).

Other names in common use include L-methionine gamma-lyase, and L-methionine methanethiol- lyase (deaminating). This enzyme participates in seven amino acid metabolism. It employs one cofactor, pyridoxal phosphate (Brown, 2019).

L-Methioninase is one of few microbial enzymes with high therapeutic value since it was reported as a potent anticancer agent against various types of tumour cell lines: breast, lung, colon, kidney, and glioblastoma. Many human cancer cell lines and primary tumours have an absolute requirement for L-methionine, an essential amino acid, to survive and proliferate. On the other hand, normal cells have the ability to grow on homocysteine, instead of methionine, due to their active methionine synthase. Many tumour cells devoid of the active methionine synthase thus depend on external methionine supplementation of the diet. Consequently, methionine is the main tumour specific target for therapeutic techniques. Thus, therapeutic exploitation of L-methioninase to deplete plasma methionine seems to be a promising strategy. Furthermore, the limited distribution of L-methioninase as intracellular enzyme among all microbial pathogens, but not in humans, makes this enzyme a promising drug target for antibacterial, antifungal, and antiprotozoal therapies. Purify L-methioninase from Candida tropicalis, Chemical and physical properties of the pure enzyme were studied. Moreover, the antitumour activity of the purified enzyme against different cancer cell lines was evaluated by (Mahsen et al., 2015).

L-methioninase in therapy and other applications:

L-Methioninase (methionineγ-lyase) has important biotechnological application because of exhibiting hydrolytic property to catalyze α-γ-elimination of L-methionine to α-ketobutyrate, methanethiol and ammonia. The abnormality behaviour of methionine based metabolic process results from ageing, obesity, Parkinson's, cardiovascular and cancer diseases among human being. The catalytic activity of L-methioninase could be used as enzyme supplementation therapy for these diseases.

L-Methioninase as an anticancer therapy:

In general, physiologically, normal cells can grow on homocysteine, instead of L-methionine, due to their active L-methionine synthase (Mecham et al., 1983). So, the cancer cells are deprived of these amino acids, they starve to death since they can't synthesize these amino acids (Lishko et al., 1993a). Nutritional starvation can be done in two ways, one by controlling the dietary intake of these amino acids and the other by decreasing the serum concentration of these amino acids. Methioninase, an enzyme that specifically degrades methionine and homocysteine, inhibits the growth of a variety of cancer cells in culture as well as solid tumours and leukaemia in animals (Tan et al., 1999; Miki et al., 2000).

Recombinant L-methionine α,γ-lyase (rMETase), an L-methionine depleting enzyme cloned from *Pseudomonas putida*, was shown to have efficacy on a broad series of cancer cell lines (Tan *et al.*, 1997). A methionine-cleaving enzyme would lower L-methionine levels more than L-methionine starvation and, thereby, could have better therapeutic effects. Studies of the anticancer efficacy of recombinant L-methioninase (rMETase) in vitro and in vivo on human tumours xenografted in nude mice pretend that all types of human tumours tested, including those from the lung, colon, kidney, brain, prostate and melanoma, were sensitive to rMETase. In contrast, normal cells were insensitive to rMETase in vitro. No toxicity was detected in vivo at the effective doses as reported by (Tan *et al.*, 1997). The most significant promise for L-methioninase, however, is most possibly in combination therapy, where it has the potential to selectively sensitize tumour cells to many classes of currently used chemotherapy. In this way, methioninase may 21 act not only as a universal cancer drug but also as a universal modulator of other chemotherapy drugs.

The enzyme is promising as an antitumour agent because L-methionine is required for the growth of malignant cells (Cellarier *et al.*, 2003). Numerous human cancer cell lines have an absolute requirement for L-methionine to survive and proliferate as an essential amino acid, whereas normal cells are L-methionine independent (Kahraman, 2015). Due to there are reports suggesting that L-methionine may be a tumour-specific target since some malignant cell lines were identified that had an absolute requirement

for L-methionine as they would not grow on homocysteine. Therefore tumours are L-methionine-dependent. On the contrary, normal cells and tissues were found to be able to use homocysteine in place of L-methionine for proliferation, and are therefore L-methionine-independent (Sundar, 2014).

Role of L-Methioninase in Food Industry:

L-methioninase has an important role in the food industry by imparting a specific aroma in variety of cheese like Limburger, camembert, blue cheeses and cheddar (Arfi et al., 2003). The enzymatic catalysis of L-methionine in presence of L yeast strains secreted a volatile sulfur component of methanethiol which has been used as flavour enhancer for cheese industry (Bonnarme et al., 2001; Selhub et al., 1995). The demethylating activity of Brevibacterium linens is used commercially as a bacterium (Weimer et al., 1999). Some yeast strains Kluyveromyces marxianus and some bacterial strains (Lactobacilli as safe organisms and used commercially as a food additive (Cuer et al.; Selhub et al., 1995).

Microbial Sources and production of L-methioninase

Enzymes are produced by fermentation using microorganisms such as bacteria or fungi under carefully controlled conditions (Schäfe et al., 2005). The first step in producing enzymes is to identify the optimal organism or host (Welt & Dinus,1994). The most common approach is to investigate plants and microorganisms found in nature, where enzymes may already be doing what is desired for an industrial application. There is a rich and broad variety of life on earth, particularly involving microorganisms (Marques et al., 2003). Research is being conducted to identify new, exciting microorganisms that already perform functions that would be valued in the industry. Some of this search has centred on extremophile microorganisms that thrive in extreme environments.

For example, volcanic vents on ocean floors create very high temperature and pressure environments where thermophilic organisms thrive. Likewise, high pH lakes in North Africa are home to many alkalophilic organisms. These organisms already produce enzymes that function in very harsh conditions and can be used to produce exciting new enzyme varieties (Marques et al., 2003). The organisms are fermented using a suitable nutrient and controlled conditions to produce the enzymes, through both intracellular or extracellular expression.

Several microbial strains having potential in the production of the enzyme have been isolated and characterized at the growth and enzyme productivity level. This led to the continuous screening program for isolation of novel microbial strains that could produce an effective enzyme with few limitations at usage sectors keeping in view (Unissa et al., 2015).

L-methioninase is resent in a wide range of organisms including, plant, bacteria, and fungi. Methioninase secreted from some bacterial species have high therapeutic value because of association with high immunogenicity and low substrate specificity. These enzymes are also used for cancer treatment by depleting supply of methionine from exogenous source to cancer cells. Cancer is an increasing cause of mortality and morbidity throughout the world. L-methionase has potential application against many types of cancers. L-Methioninase is an intra-cellular enzyme in bacterial species, an extra-cellular enzyme in fungi, and absent in mammals (Kharayat and Singh, 2018).

Microbial L-methioninase has received much attention since it shows anti-proliferative activity towards various types of malignant cells (Cellarier et al. 2003). Consequently, these cells are auxotrophic for L-methionine, depending absolutely on the exogenous supply of L-methionine for their survival and proliferation (Kokkinakis et al. 1997), whereas normal cells are relatively resistant to exogenous L-methionine restriction because it contains active methionine synthase (Bergstorm et al. 1987).

Therapeutic efficiency of bacterial L-methioninase has rarely occurred without some evidence of toxicity and immunogenic reactions, especially with regard to multiple doses (Tan et al. 1997). Therapeutic efficiency of fungal L-methioninase occurs with fewer immunogenic and allergic reactions, which may be attributed to the higher specificity of their substrates compared with the substrate analogues, displaying fewer problems during the course of tumour therapy (Hawkins et al. 2004).

L-methioninase of microorganisms was studied from microbes were isolated from terrestrial and marine samples (Suganya et al., 2017). The microbial sources of the enzyme as:

1-Bacteria

L-methioninase has been reported from both gram-positive and gram-negative bacterial species from various sources (Rodionov et al., 2004), some of which are anaerobic Porphyromonas gingivalis (Yoshimura et al., 2000) and Treponema denticola (Sharma et al., 2014), in eukaryotic pathogens such as Entamoeba histolytica (Tokoro et al., 2003), farther more, the bacteria as Pseudomonas putida, Aeromonas sp., Citrobacter freundii and Lactococcus lactis (Swathi, 2015); Clostridium sporogenes (Krishnaveni et al., 2009); Salmonella, Mycobacterium, Bacillus, Listeria (Bernardes et al., 2010) and Brevibacterium linens (Pavani and Saradhi, 2014). L-methioninase from many bacterial species was purified and characterized from several microorganisms such as B. subtilis, Aeromonas sp., C. freundii, B. linens, L.

lactis and Clo. sporogenes (El-Sayed, 2010; El-Sayed and Shindia, 2011; Singh and Kharayat, 2018).

L-methioninase has been found in bacteria, some of which are anaerobic, Porphyromonas gingivalis (Yoshimura et al., 2000) and Treponema denticola (Fukamachi et al., 2005). L-methioninase have been isolated, purified, and characterized from several bacterial sp. such as P. putida (El-Sayed, 2010; Esaki and Soda, 1987; Esaki et al., 1979; Ito et al., 1976; Lishko et al., 1993b; Nakayama et al., 1984; Tanaka et al., 1977; Tanaka et al., 1976), Clo. sporogenes (Tanaka et al., 1977), Aeromonas sp. (Nakayma et al., 1984), Citrobacter intermedius (Faleev et al., 1996), B. linens (Dias and Weimer, 1998) Trichomonas vaginalis (Lockwood and Coombs, 1991) and Porphyromonas gingivalis (Yoshimura et al., 2000). Pinnamaneni et al. (2012) found B. linens which are a normal flora present in the whey of curd are a rich source of L-methionine γ-lyase (MGL). When L-methioninase discovered in Escherichia coli, a series of research has been carried out to explore the enzyme and this enzyme has been found in various bacteria and is considered as a key enzyme in the bacterial metabolism of L-methionine (Takakura et al., 2006).

Actinomycetes:

Selim et al. (2015) Found that, only 60 isolates of Streptomyces tested; only 40 isolates were capable of utilizing L-methionine as the only main origin of nitrogen in the medium. Also, 24 of these isolates could grow in medium amended with L-methionine as a source of nitrogen and carbon, the enzyme purified from the crude extract of Streptomyces sp. DMMMH4.

Forty-five Streptomycetes isolates were screened for production of L-methioninase. Among them, the best nine isolates have a higher productive of extracellular L-methioninase. These isolates were quantitatively checked of L-methioninase production and the promising isolate was subjected to identification showed that the strain named Streptomyces variabilis 3MA2016 (El Awady et al., 2017). Actinomycetes as Streptomyces sp. (Abdelraof et al., 2019; Khalaf and El-Sayed, 2009; Nwachukwu and Ekwealor, 2009).

Filamentous Fungi and yeast:

Production and optimization of extra-cellular L-methioninase enzyme were investigated by Swathi (2015) using several agro-industrial residues by Aspergillus flavipes MTCC 6337 using solid-state fermentation (SSF). Fungal species as an intracellular and extracellular enzyme (El-Sayed, 2009). Fungi such as Trichoderma harzianum (Salim et al., 2019), Geotrichum candidum (Bonnarme et al., 2001) and Penicillium notatum (Khalaf and El-Sayed, 2009); archaea as Ferroplasma acidarmanus (Baumler et al., 2007) and the protozoan Entamoeba histolytica (Sato et al., 2006).

Some studies were reported on the partial characterization of L-methioninase from fungi including Penicillium sp., Aspergillus sp., Humicola fuscoatra and A. flavipes (Swathi, 2015), describe filtrates L-methioninase in the culture of yeast such as Geotrichum candidum, Debaromyces hansenii and Saccharomyces cerevisiae (Bonnarme et al., 2001). It is noteworthy that reports describe L-methioninase in the culture filtrates of a few yeasts including Geotrichem candidum, Debaromyces hasenii and Saccharomyces cerevisiae (Bonnarme et al., 2001). A large number of isolated yeast from various locations including Egyptian soils, marine water or cheese products were quantitatively screened for their L-methioninase activity. Candida tropicalis was the most active isolate. Results showed that the enzyme was intracellular produced (Selim et al., 2015). Sharma et al., 2014, described L-methioninase in the culture filtrates of a few yeasts including Geotrichem candidum, Debaromyces hasenii and Saccharomyces cerevisiae.

Fungi produce Enzymes surrounds the soil particles and glues macroaggregate soil particles together and gives soil its structure and useful in several applications (Binod et al., 2017). Among the microorganisms, fungi and bacteria They are the most important producers of bioactive secondary metabolites. They produce vitamins, enzymes, antitumour agents, immunodefying agents and mainly antibiotic compounds. Enzymes are found in animal, plant sources and microorganism. bacteria, fungi, yeast, actinomycetes, algae and plants etc. (El- Sayed, et al., 2010 and Unissa et al, 2015).

Some microbial production using organic wastes

With growing population, demands of agro-industrial products are increasing exponentially. To meet this high demand, an increased quantity of food products is being produced, leaving an elevated level of agro-industrial wastes. It has been reported that approximately 998 million tons of agricultural wastes are produced yearly all over the world (Agamuthu, 2009).

A large number of by-products or wastes are produced worldwide through various food industries. These wastes cause a serious disposable problem with the environment. So, now a day's different approaches are used for alternative use of these wastes because these by-products are an excellent source of various bioactive components.

The contents of synthetic media are very an expensive and these contents might be replaced with more economically available agro-industrial wastes (Ikram-ul-Haq et al., 2003; Ramachandran et al., 2007; Queiroz et al.,2016).

Most of the commercial enzymes are extracellular enzymes such as proteolytic enzymes.

Diverse groups of microorganisms, including fungi, yeasts and bacteria synthesize these enzymes, of the industrial enzymes, 75% are hydrolytic enzymes (Dias et al., 2008).

Organic waste can be practically defined as any material or unused by-product from a process that is biodegradable and comes from either plant or animal. The composition of organic waste varies from the nature of the original material. Depending on the type of organic waste, SSF can be applied with the aim of producing different valuable bio-products (Pandey et al., 2000; El-Bakry et al., 2015; Dave et al., 2012; Motta, Santana, 2014).

Food waste, from kitchen, canteen, food-processing and restaurant waste, is an essential component of municipal solid waste (MSW) and its production has become a global concern (Ren et al., 2017). According to FAO (2012), about 1.3 billion tons of food in the form of fruits, bakery, bread, vegetables, dairy products, and meat are lost every year through food supply chain worldwide. With increasing population, economic growth and living standards, the food waste are projected to further increase in the next 25 years (Kiran et al., 2014). The conventional methods of waste treatment like composting, incineration, animal feed production and anaerobic digestion (AD) are used to manage food waste (Thi et al., 2015). Food waste is a rich source of various vital components such as protein, carbohydrate (hemicellulose, cellulose, starch, and sugar like sucrose, fructose, and glucose), oil, mineral, and fat that can be used in a wide range of enzymatic and microbial processes (Pham et al., 2015).

Microbial production of L-methioninase using organic wastes:

Presence of L-methioninase has been reported in several organisms including plants as Arabidopsis thaliana (Rébeillé et al., 2006).

Optimal culture conditions and diverse methods have been reported for the production and purification of L-methioninase from various organisms include solid-state fermentation (SSF) by using several agro-industrial residues: corn, tea waste, soya bean, palm oil, sesame oil and wheat bran. At the same time, L-methioninase can be done by submerged fermentation (SMF) (Abu-Tahon and Isaac, 2016; Khalaf and El-Sayed, 2009).

The natural agro-industrial residues were utilized as substrates for enzyme production and it's a favoured environmentally and economically. For the high expense of enzyme purification from the microbial cultures, immobilization is a promising technique for enzyme stabilization and continuous production of methanethiol (El-Sayed and Shindia, 2011). Permeabilization treatment proved that L-methioninase was found to be extracellularly produced in bacteria (Selim et al., 2015; Swathi, 2015).

L-methioninase production by fungi under submerged fermentation (SMF) by Aspergillus sp. (Ruiz-Herrera and Starkey 1969b), Debaromycs hanseni (Bonnarme et al. 2001), A. flavipes (Khalaf and El-Sayed 2009) has been reported. SSF has also been reported for its production by A. flavus (El-Sayed 2009). Physiologically L-methionine can be rapidly oxidized through Millard reactions forming Amador compounds that consequently reduce their bioavailability as carbon and nitrogen for the organism (Delgado-Andrade et al. 2007). Thus, using L-methionine as a substrate for enzyme induction could be, at least technically, not the superior substrate, in addition to the economic expense of these medium components (El-Sayed 2010). Consequently, the search for novel producers and new forms of the growth medium for large scale production for this enzyme will be a challenge. SSF on agro-industrial residues promises a cost-effective bioprocess as it requires small vessels and gives a higher yield (El-Sayed 2009). SSF for the enzyme production employing methionine-containing solid substrates displayed a more stable physical form of bounded methionine that could be a new strategy from the technical and economical points of views (El-Sayed 2009). Practically no comprehensive studies on the potential of filamentous fungi for the L-methioninase production (Khalaf and El-Sayed 2009).

Aspergillus ustus AUMC 10151 displayed the highest yield of the enzyme, followed by A. ochraceus and Fusarium proliferatum upon optimization of the submerged fermentation (SMF) conditions, the maximum enzyme yield and seven agro-industrial by-products were screened as substrates for L-methioninase production under solid-state fermentation (SSF). High amounts of L-methioninase was produced when wheat bran, followed by rice bran and soya bean meal (Abu-Tahon and Isaac, 2016). The production and optimization of extracellular L-methioninase enzyme using several agro-industrial residues by Aspergillus flavipes MTCC 6337. The organism produced high levels of L-methioninase under optimized culture conditions (Swathi, 2015). Some factors influencing L-methioninase production by Candida tropicalis isolate (Mohsen et al., 2013).

References:

1. Abu-Tahon, M. A. and Isaac, G. S. (2016). Comparative study of a new alkaline L-methioninase production by *Aspergillus ustus* AUMC 10151 in submerged and solid-state fermentation. *Brazilian Archives of Biology and Technology, 59*.

2. Bahl, C.; Saxena, S. G. and Sharma, S. G. (2012). *Screening endophytic fungal broth for l-Methioninase activity*.
3. Baylln, S.B., Herman, J.G., Graff, J.R., Vertino, P.M. and Issa, J.P., 1997. Alterations in DNA methylation: a fundamental aspect of neoplasia. In Advances in cancer research, 72, pp. 141-196. Academic Press.
4. Bondar DC, Beckerich JM, Bonnarme P. Involvement of a branched-chain aminotransferase in production of volatile sulfur compounds in Yarrowia lipolytica. Applied and Environmental Microbiology 2005; 71:4585-4591.
5. Bonnarme P, Lapadatescu C, Yvon M, Spinnler HE. Lmethionine degradation potentialities of cheese-ripening microorganisms. Journal of Dairy Research. 2001; 68:663-674.
6. Buonaurio, R.; Stravato, V. and Cappelli, C. (2001). Brown spot caused by Sphingomonas sp. on yellow Spanish melon fruits in Spain. *Plant pathology, 50*(3), 397-401.
7. Davis, C.D. and Uthus, E.O., 2004. DNA methylation, cancer susceptibility, and nutrient interactions. Experimental Biology and Medicine, 229(10), pp.988-995.
8. El‐Sayed, A. S. (2009). L‐methioninase production by *Aspergillus flavipes* under solid‐state fermentation. *Journal of basic microbiology, 49*(4), 331-341.
9. El-Sayed AS. Microbial L-methioninase: production, molecular characterization, and therapeutic applications. Applied Microbiology and Biotechnology 2010; 86:445467.
10. El-Sayed, A. S. and Shindia, A. A. (2011). PLP-Dependent Enzymes: a Potent Therapeutic Approach for Cancer and Cardiovascular Diseases. In *Targets in Gene Therapy*: In Tech.
11. Goseki, N., Yamazaki, S., Shimojyu, K., Kando, F., Maruyama, M., Endo, M., Koike, M. and Takahashi, H., 1995. Synergistic effect of methionine‐depleting total parenteral nutrition with 5‐fluorouracil on human gastric cancer: a randomized, prospective clinical trial. Cancer Science, 86(5), pp.484-489.
12. Guo, H., Lishko, V.K., Herrera, H., Groce, A., Kubota, T. and Hoffman, R.M., 1993. Therapeutic tumorspecific cell cycle block induced by methionine starvation in vivo. Cancer research, 53(23), pp.5676- 5679.
13. Hoffman RM (1984). Altered methionine metabolism, DNA methylation and oncogene expression in carcinogenesis. Biochem. Biophys. Acta 738:49-87.
14. Imada, A.; Igarasi, S.; Nakahama, K. and Isono, M. (1973). Asparaginase and glutaminase activities of micro-organisms. *Microbiology, 76*(1), 85-99.
15. Kallio, R.E. and Larson, A.D., 1955. Methionine degradation by a species of Pseudomonas. In A symposium on amino acid metabolism. Johns Hopkins Press, Baltimore, pp. 616-631.
16. Khalaf, S. A. and El-Sayed, A. S. (2009). L-Methioninase production by filamentous fungi: I-screening and optimization under submerged conditions. *Current microbiology, 58*(3), 219-226.
17. Kokkinakis, D.M., Hoffman, R.M., Frenkel, E.P., Wick, J.B., Han, Q., Xu, M., Tan, Y. and Schold, S.C., 2001. Synergy between methionine stress and chemotherapy in the treatment of brain tumor xenografts in athymic mice. Cancer Research, 61(10), pp.4017-4023.
18. Lockwood, B. C. and Coombs, G. H. (1991). Purification and characterization of methionine γ-lyase from Trichomonas vaginalis. *Biochemical Journal, 279*(3), 675-682.
19. McCoy, T. A., Maxwell, M., and Kruse, P. F. (1959). The amino acid requirements of the Jensen sarcoma in vitro. *Cancer Res*, *19*(6 Pt 1), 591-595.
20. Ohnuma, T., Waligunda, J., and Holland, J. F. (1971). Amino acid requirements in vitro of human leukemic cells. *Cancer research*, *31*(11), 1640-1644.
21. Paul, G. C.; Kent, C. and Thomas, C. (1994). Hyphal vocuolation and fragmentation inpenicillium chrysogenum. *Biotechnology and bioengineering, 44*(5), 655-660.
22. Raimbault, M. and Alazard, D. (1980). Culture method to study fungal growth in solid fermentation. *European Journal of Applied Microbiology and Biotechnology, 9*(3), 199-209.
23. Ruiz-Herrera, J. and Starkey, R. L. (1969a). Dissimilation of methionine by a demethiolase of Aspergillus species. *Journal of bacteriology, 99*(3), 764-770.
24. Ruiz-Herrera, J. and Starkey, R. L. (1969b). Dissimilation of methionine by fungi. *Journal of bacteriology, 99*(2), 544-551.
25. Selim, M.; Elshikh, H.; El-Hadedy, D.; Saad, M.; Eliwa, E. and Abdelraof, M. (2015). L-Methioninase from some *Streptomyces* isolates I: Isolation, identification of best producers and some properties of the crude enzyme produced. *Journal of Genetic Engineering and Biotechnology, 13*(2), 129-137.
26. Sharma, B., Singh, S. and Kanwar, S.S., 2014. Lmethionase: a therapeutic enzyme to treat

malignancies. BioMed research international, 2014.
27. Sharma, D.; Niwas, S. and Behera, B. (1991). Solid state fermentation of bagasse for the production of cellulase enzyme from cellulolytic fungi and extent of simultaneous production of reducing sugars in the fermenter. *Journal of Microbial Biotechnology, 6*(1), 7-14.
28. Sun, X., Yang, Z., Li, S., Tan, Y., Zhang, N., Wang, X., Yagi, S., Yoshioka, T., Takimoto, A., Mitsushima, K. and Suginaka, A., 2003. In vivo efficacy of recombinant methioninase is enhanced by the combination of polyethylene glycol conjugation and pyridoxal 5′- phosphate supplementation. Cancer research, 63(23), pp.8377-8383.
29. Tan, Y., Sun, X., Xu, M., An, Z., Tan, X., Tan, X., Han, Q., Miljkovic, D.A., Yang, M. and Hoffman, R.M., 1998. Polyethylene glycol conjugation of recombinant methioninase for cancer therapy. Protein Expression and Purification, 12(1), pp.45-52.
30. Theantana, T.; Hyde, K. and Lumyong, S. (2007). Asparaginase production by endophytic fungi isolated from some Thai medicinal plants. *KMITL Science and Technology Journal, 7.31*, 13-18.
31. Kokkinakis DM, Schold Jr SC, Hori H, Nobori T. Effect of long‐term depletion of plasma methionine on the growth and survival of human brain tumor xenografts in athymic mice. Nutrition and Cancer 1997; 29:195-204. 6.
32. Mangum JH, North JA, Vitamin B. dependent methionine biosynthesis in HEp-2 cells. Biochemical and Biophysical Research Communications 1968; 32:105-110.

3/30/2020