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Review

Dietary Inclusions and Exclusions: Preparation Against Cancer

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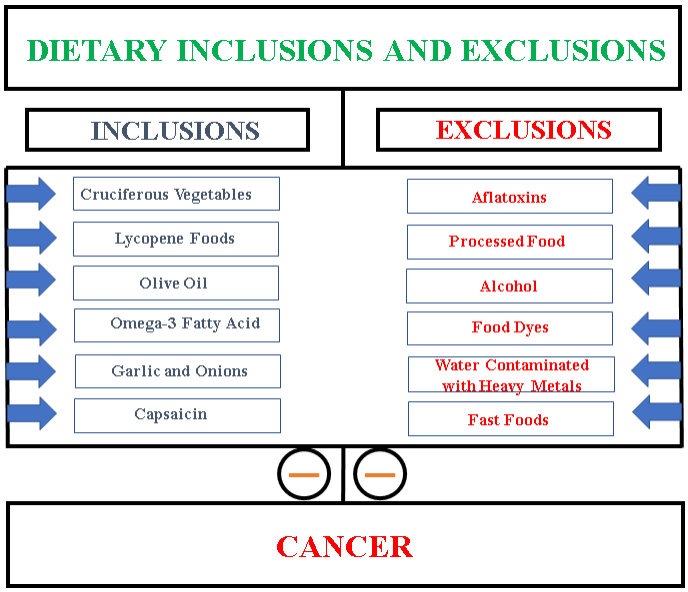
Abstract: Cancer results due to an imbalance between regulation of cell proliferation and apoptosis. As per the latest data released by World Health Organization (WHO), a large part of global population cannot access proper anti-cancer therapy, and this imposes a burden of approximately US$ 1.16 trillion on global economy. Relevant studies were identified through electronic searches of Pubmed, Medline, Scopus, Google scholar. In this review, we found that there is extensive range of dietary items whose components can influence either cell proliferation rate or cell death rate or both. Exclusion and avoidance of several dietary items/habits are linked with reduced risk of several types of cancer. In addition, many dietary items have been proven beneficial for minimizing the risk of various cancers and slow down their progression. More extensive clinical studies are required for establishing quantitative facts about dose-response relationship.

Keywords: Diet; cancer; fast food; vegetables; dietary inclusions; dietary exclusions

Graphical Abstract:



1 Introduction

World Health Organization (WHO) defines cancer as "a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs." As per WHO fact sheet released in September 2018, 9.6 million people

worldwide were estimated to die from cancer in 2018. Around 30–50% of cancers can be prevented by opting healthy lifestyles [1]. Below mentioned facts recorded by WHO warn us to explore nonpharmacological approaches against this demon. Globally, 1 in 6 people die from cancer. Lung, liver, stomach, colorectal and prostate cancers are five most common fatal cancers found in men. Moreover, breast, lung, colorectal, cervical and stomach are the most responsible cancers for women mortality. Only about 30% of low-income countries are able to provide effective anti-cancer treatment. The annual burden on global economy due to cost of cancer is approximately US$ 1.16 trillion. Non-pharmacological approaches like healthy dietary habits and regular physical activity should be promoted as adjunct to conventional anti-cancer therapies to reduce economic burden and improve quality of life. In this review, we found that there is extensive range of dietary items whose components can influence either cell proliferation rate or cell death rate or both. Exclusion and avoidance of some dietary items/habits may reduce risk of several types of cancer. In addition, inclusion of many items in diet has been proven beneficial for minimizing the risk of various cancers and slow down their progression.

2 Methods

Relevant studies were identified through electronic searches of Pubmed, Medline, Scopus, Google scholar. The search used the terms "carcinogenic potential," "fat diet and cancer risk, "fast food and cancer risk," "water contaminants and cancer risk," "anticancer potential of fruits and vegetables." In addition, we searched the bibliographies of relevant studies, reviews, and editorial letters.

3 Dietary Items and Habits that Increase Risk of Cancer

Several studies have explored the link between diet and certain cancers including breast, prostate and colorectal cancer [2–4]. Some epidemiological evidence has shown that those who consume very fewer fruits and vegetables have a high risk of cancer in comparison with those who consume good amount of the same. 128 out of 156 dietary studies reported statistically eloquent protective effects of consuming fruits and vegetables against cancer [5]. It indicates towards inverse relationship between intake of fruits and vegetables with risk of several cancers. Scientific investigations have found that exposure of many additives (nitrates and nitrites); food contaminants and dietary components have carcinogenic potential [6,7]. People are failing to extract time for their health wellness. Even they do not hesitate to compromise their health while buying and eating packaged, processed or artificially colored food. A study has revealed the occurrence of 80% of colorectal cancer due to dietary reasons [8]. Further, Jamal and colleagues estimated that colorectal cancer is third and second most identified cancer in males and females respectively [9].

3.1 Aflatoxins

These are toxic metabolites of certain fungi. *Aspergillus flavus* is one of the famous sources of aflatoxin that can infect many nuts and grains. Milk produced by mammals eating this infected food stuff can pass aflatoxins to their infants [6]. According to a report published by department of food safety and zoonoses of world health organization [10] in 2018, people who get exposed to aflatoxin B_1 for the long term become more vulnerable to get suffered from liver and kidney cancer. The suggested mechanism of hepatocellular carcinoma caused due to Aflatoxin B_1 [11] is depicted in Fig. 1. It shows AFBO (metabolite of aflatoxin B_1) can cause mutation of p53 gene (a tumor suppressor gene) that may result in hepatocellular carcinoma.

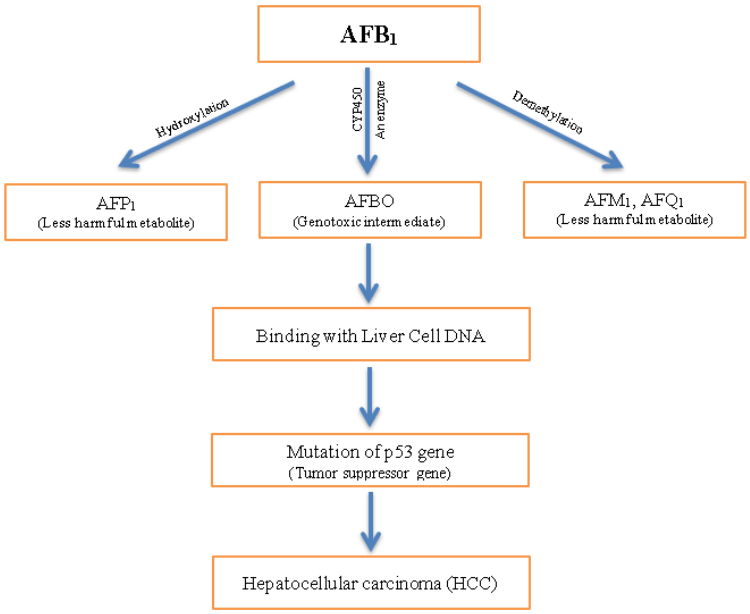


Figure 1: Pathogenesis of hepatocellular carcinoma caused by aflatoxin (AFB_1)

3.2 Processed Food

A study on the Chinese population showed a significant link between consumption of salted meat, pickled vegetables and increased risk of gastric cancer. Reduced intake of salt processed foods may reduce the chances of getting gastric, colon, rectum, pancreas, lung, bladder cancer [12,13]. High-temperature processing, barbecuing of meat initiates reaction between amino acids and sugars (Maillard reaction) that results in production of heterocyclic amines (HACs) like 2-Amino-3, 8-dimethyl imidazo-[4,5f] quinoxaline (MeIQx) and the 2-Amino-1-methyl6 phenylimidazo [4,5b] pyridine (PhIP) which are classified as potential carcinogenic compounds for human international Agency for Research on Cancer (IARC). Incomplete combustion of oil or cooking food by smoking produces polycyclic aromatic hydrocarbons (PHAs) like benzo[a] pyrene which is a potential carcinogen. DNA mutation is the suggested reason for carcinogenesis caused by PHAs and HACs [14].

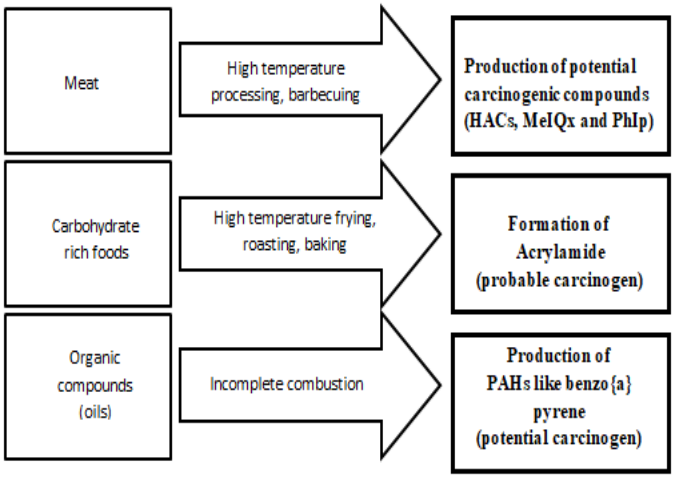


Figure 2: Possible carcinogenic effects of processed foods

High (120°C or above) temperature [15] frying, roasting, baking of carbohydrate-rich foods result in formation of acrylamide [16,17]. Dietary exposure to acrylamide in Chinese elderly population exhibited increase in overall cancer mortality [18] and therefore acrylamide is classified as "probable human carcinogen" by IARC. These harmful effects are shown in Fig. 2.

Some epidemiological studies have reported that during high-temperature cooking, grilling meat (containing heme present in myoglobin and hemoglobin) undergoes lipid peroxidation and oxidative stress and consequently few genotoxic aldehydes like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) get formed which enhance cancer progression [19–21] and the same can be understood by Fig. 3.

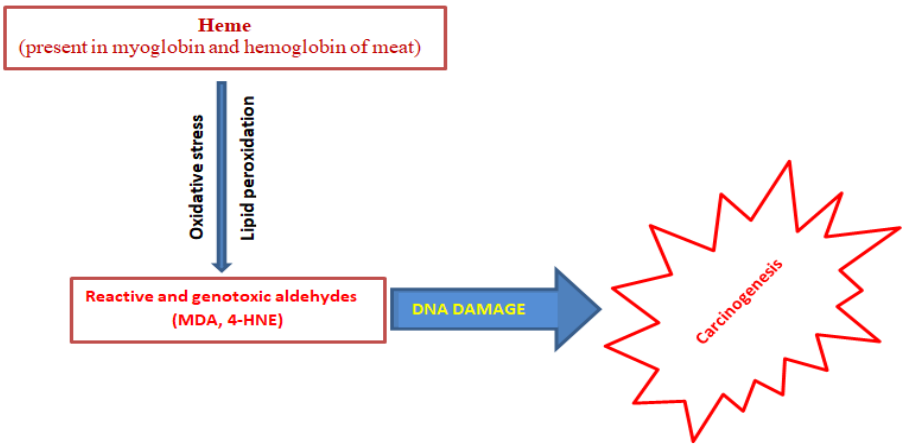


Figure 3: Mechanism of carcinogenesis induced by high-temperature cooking of meat

3.3 Acetaldehyde

Humans may get acetaldehyde exposure from various foods, metabolism of ethanol. Binding to DNA acetaldehyde forms stable DNA adducts and also interferes with DNA repair processes which may promote carcinogenesis [22]. With sound evidence, heavy drinkers are known to be highly vulnerable to mucosal hyperproliferation of upper aerodigestive tract [22], large intestine [23], and cancers of upper respiratory tract [6,24].

3.4 Food Dyes: Colorful Carcinogens

People are more affectionate for colorful food servings but till when they are not aware of possible risks. But food dyes like Blue1, Blue2, Citrus Red2, Green3, Orange B, Red3, Yellow6 have been found to cause kidney, bladder, thyroid, brain, adrenal and testicular tumors in rodent studies [25]. Clinical studies are needed to investigate the effects on humans.

3.5 Drinking Water Contaminated with Heavy Metals

In some Indian states (Uttar Pradesh, Bihar, West Bengal, Assam) cities situated in close proximity to the Ganga river and its subsidiaries, high levels of heavy metals have been noted [26]. Heavy metals (mercury, arsenic, lead, cadmium, chromium) induce generation of reactive oxygen species which can cause DNA lesions and subsequently promote carcinogenesis [27]. Histopathology reports and spectrophotometric assessment of gall bladder cancer patients living in those areas confirmed elevated levels of heavy metals like arsenic, mercury, lead, cadmium, and chromium in affected tissues and bile. These findings indicate towards link of heavy metal with gall bladder cancer [28].

3.6 Fast Foods

Fried fast foods, sweetened drinks and other foods with a high glycemic index are noted to increase the risk of colorectal cancer [29]. It has been observed that high consumption of fast foods containing high

fat may lead to accumulation of polycyclic aromatic hydrocarbons (PAHs) and the intestine is most affected part of gastrointestinal tract by fats [30]. These findings point towards increasing serious risk of development of cancer with frequency of fast-food intake.

4 Foods/Dietary Habits that Decrease the Risk and/or Slow Down Progression of Cancer

Studies suggest that appropriate intake of adequate quantities of phytoestrogens, selenium, methylcobalamin (Vitamin B_{12}), Folic acid, Vitamin D, C, E, and carotene may reduce cancer risk up to 60% and speeds up recovery as well [31].

4.1 Cruciferous Vegetables

These vegetables (Broccoli, Cauliflower, Bok choy, Brussels sprouts, Cabbage) come from plants of the family known as Cruciferae or Brassicaceae. Cruciferous vegetables [32] are rich sources of sulfur-containing compounds like glucosinolates and hydrolysis of these compounds during chopping and chewing of cruciferous vegetables result in products like indole-3-carbinol (I3C) and isothiocyanates Tab. 1 [33–36].

Table 1: Cancer preventing effects of compounds found in cruciferous vegetables

S. No.	Compound found in cruciferous vegetables/ it's metabolite	Cancer sample/cell lines used in the study	Suggested mechanisms	References
1.	Indole-3 carbinol (I3C)	Human cell lines, $Wwp1^{-/-}$ mice and its paired $Wwp1^{+/+}$ mice	Reactivation of a potent tumor suppressor gene PTEN (Phosphatase and tensin homolog) through inhibition of WWP1(WW Domain Containing E3 Ubiquitin Protein Ligase 1)	[33]
2.	Indole-3 carbinol (I3C)	human breast tumor cell line MDA MB468	inhibits protein kinase B/Akt and induces apoptosis	[34]
3.	3,3'-diindolylmethane (DIM)	Human breast adenocarcinoma cell lines MCF-7 (estrogen dependent) and MDA-MB-231 (estrogen independent)	Increases p21 protein and mRNA levels and induce G_1 cell-cycle arrest	[35]
4.	Indole-3 carbinol (I3C)	Human prostate cancer cell line PC-3	G1 cell cycle cessation PC-3 cells due to changes occurred in G1 cell cycle proteins	[36]

4.2 Lycopene Foods

Lycopene (a red carotenoid) is abundantly found in ripe tomatoes, red watermelon and grapefruits. It prevents oxidative damage of DNA by fighting against free radicles and in this way, it slows the transformation of normal cells to cancerous cells. Voluminous evidence about its anti-oxidant, anti-proliferative, pro-apoptotic activities against oral and prostate cancer are available [37–40]. Some other noted anticancer effects of lycopene are listed in Tab. 2 and Tab. 3 [41–46].

Table 2: Anticancer effects of lycopene

S. No.	Cancer sample/cell lines used in the study	Suggested mechanism	References
1.	Human gastric HGC-27 cell line	G0-G1 cell cycle arrest, apoptosis via significant suppression of ERK (extracellular signal-regulated kinase) signalling pathway	[41]

2.	Androgen independent DU145, PC-3, and androgen-dependent LNCaP human prostate cancer cells	Cell growth arrest and apoptosis (depending on dose)	[42]
3.	Human prostate, breast, colon, liver, larynx, and cervical cancer lines (DU145, HT-29, MCF-7, Hep-G2, Hela, Hep-2 cell lines)	Cell cycle arrest, increase in apoptosis, inhibition of cell proliferation	[43]

Table 3: Lycopene abundance in food items

S. No.	Lycopene source	Quantity present (mg/100g)	References
1.	Apricot	0.01–0.05	
2.	Fresh tomatoes	0.7–20	
3.	Fresh papaya	2.0–5.30	
4.	Cooked tomatoes	3.7	[44–46]
5.	Fresh watermelon	2.3–7.2	
6.	Pink guava	5.2–5.5	
7.	Pink grapefruit	0.4–3.4	

4.3 Olive Oil (Olea Europaea, Oleaceae)

It is a blend of oleic acid, linoleic acid, secoiridoids, squalene, tyrosol, hydroxytyrosol (HT), lignans, flavonoids, triterpenes, β-sitosterol [47]. Refining process makes the olive oil lacking polyphenols, vitamins, and phytosterols [48]. And high abundance of polyphenols is evident in extra virgin olive oil [49]. Extra virgin olive oil is obtained from olives by pressing them without heat and chemical treatment. In Mediterranean region olives are freely consumed and olive oil is cooking fat of choice; and epidemiological studies relate this liberal consumption of olive oil with significantly fewer incidences of colorectal, breast and skin cancer [47,50] in this region. Furthermore, squalene (abundantly found in Olive oil) is known for the tumor-inhibiting property [50]. Some evident biological effects of olive polyphenols suggesting their use in cancer prevention are listed in Tab. 4 [51–55].

Table 4: Mechanisms of cancer-preventing effects of olive oil constituent

S. No.	Name of olive polyphenol	Sample/cell lines used	Biological effects observed	References
1.	Oleuropein	Human umbilical vein endothelial cells	• Reduced angiogenesis	[51]
2.	Oleuropein	MDA-MB-231 and MCF-7 human breast cancer cell lines	• Apoptosis induction via the mitochondrial pathway • Cell cycle delay at S phase • Inhibit pro-proliferation protein NF- κB and cyclin D1	[52]
3.	Oleocanthal	Human breast cancer MDA-MB-231, MCF-7, and T-47D cells	• Cytotoxicity • Inhibition of phosphorylation of mammalian target of rapamycin	[53]

4.	Oleocanthal	Human prostate cancer PC-3 cells and Human pancreas adenocarcinoma BxPC3 cells	• Induction of apoptosis, • Activation of ERK ½ signalling • Inhibition of acid sphingomyelinase • Induction of lysosomal membrane permeabilization	[54]
5.	Hydroxytyrosol	Estrogen receptor-negative SKBR3 breast cancer cell	• Apoptosis induction	[55]

4.4 Foods Containing Omega-3 Fatty Acid

Nowadays, several cancer researchers have started exploring apoptosis (natural cell death) as a target for anticancer therapy and they have noted overexpression of antiapoptotic proteins and under-expression of proapoptotic proteins in cancer cases [56]. Reports also claim that disturbed apoptosis circuitry is highly associated with oncogenicity [57]. PUFAs such as omega-3 fatty acids including Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can inhibit growth of cancer cells and induce apoptosis both in-vivo and *in-vitro*. Furthermore, these polyunsaturated fatty acids are found valuable [58,59] for cancer prevention and improving the efficacy of certain antineoplastic drugs [60]. These findings are consistent with some previously reported drug sensitizing effects of DHA and EPA by inducing selective cancer cell death as mentioned in Tab. 5 [61–67].

Table 5: Proven effects of EPA and DHA on chemo-sensitivity of malignancies/cell lines to anticancer drugs

S. No.	DHA	EPA	Malignancy type/Cell lines	Chemotherapy drug (s)	Suggested mechanisms	References
1.	#	#	Gastric cancer	Cisplatin	↑Apoptosis, Activation of ADORA1	[61]
2.	*	#	TE-1 oesophageal cancer cells	Paclitaxel, Docitaxel, Cisplatin	↑Antiproliferative effects ↑Apoptosis	[62]
3.	#	#	A 549 lung cancer cells	Doxorubicin	↓PGE_2 levels, ↑ROS	[63]
4.	#	#	MEC-2 B-PLL-derived cell line JVM-2 and B-CLL-derived cell lines EHEB and	Fludarabine Doxorebicin Vincristine	↑Apoptosis ↑ROS production ↓Viability	[64]
5.	#	*	Bcr-Abl expressing HL-60 cells	Imatinib	↓Membrane integrity ↓Viability, ↑Apoptosis	[65]
6.	#	*	HTLV-I–immortalized and –transformed T cells (a model of adult T-cell leukemia/lymphoma)	Arsenic trioxide	↑Cell death, ↓Proliferation, ↑ROS production, Inhibition of Akt and AP-1	[66]
7.	*	#	HL-60 myeloid leukemia cell line	12-O-tetradecanoylphorbol-13-acetate	↑ROS production ↑Differentiation of myeloid leukemia cells	[67]

(# Effects proven in study, * Effects not proven/not tested in study)

4.5 Garlic and Onions (Allium Genus Vegetables)

A large number of epidemiological studies have provided strong evidence in favor of cancer (especially gastrointestinal and esophageal) preventing effects of *Allium* genus vegetables including garlic and onions [68–70]. Heating badly influences the anticancer property of garlic as it has been noted that microwaving for 60 seconds or 45 minutes oven heating of uncrushed garlic leads to significant weakening of anticancer effect exhibited by garlic [71]. A 2016 study on Chinese lung cancer patients suggested the significant inverse association of raw garlic intake with development of lung cancer in a dose-dependent manner when compared to no intake [72]. It has been proved that garlic extract augments the anticancer effect of existing antineoplastic drugs such as cisplatin, docetaxel and gemcitabine [69].

4.6 Capsaicin

Pungent phytochemical capsaicin present in peppers (widely used spices) is well known for having anti-oxidant and anti-inflammatory potential [73]. Capsaicin has been explored and proved to have anticancer property by altering expression of some genes involved in angiogenesis, cancer cell survival, growth arrest [74,75]. Capsaicin strengthens the fight against human glioma [76], myeloma [77], osteosarcoma [78] and colorectal [79], lung [80], bladder [81], stomach [82] cancers by accelerating apoptosis rate [76,83]. Some noted anticancer activities of capsaicin are summarized in Tab. 6 [76,81,84,85].

Table 6: Mechanisms of cancer-preventing effects of capsaicin

S. No.	Sample/ cell line studied	Suggested mechanisms	References
1.	Human small cell lung cancer cell lines (NCI-H82, NCI-H69, DMS53, DMS114)	Induces TRPV6 receptor and calpain pathway-mediated apoptosis	[84]
2.	Human KB cancer cells	Cell cycle arrest at G2/M phase Dissipation of mitochondrial membrane potential	[85]
3.	Human urothelial cancer cells	Induction of Fas/CD95 mediated apoptosis	[81]
4.	Human glioma cells	Induction of TRPV1 vanilloid receptor-mediated apoptosis	[76]

5 Conclusion and Future Directions

In this review, we conclude that the risk of several cancers may get significantly increased due to chronic intake of various processed food, few food colors, infected nuts, drinking water containing heavy metals beyond permissible limits. Histopathological investigations of cancer patients have revealed the association of dietary habits and cancer risk. The second part of this review is focused on non-pharmacological approaches like healthy and dietary intake and physical active lifestyle to ameliorate the risk of various cancers by providing the evidence well noted in scientific literature. Dieticians and nurses must utilize teachable moments to educate patients and attendants on the importance of diet and active lifestyle for developing immunity against cancer. We recommend extensive quantitative analysis of dietary items for their carcinogenic or anticancer potential. And based on these results, advisories could be framed for restrictions or promotions of sale of dietary items for the purpose of cancer prevention.

Abbreviations Used: AFB_1: Aflatoxin B_1; **CD-95:** Cluster of differentiation 95; **DHA:** Docosahexaenoic acid; **DNA:** Deoxyribonucleic acid; **EPA:** Eicosapentaenoic acid; **ERK:** Extracellular signal-regulated kinase; **HACs:** Heterocyclic amines; **HGC:** Human gastric cancer; **HL:** Human leukaemia; **HT:** Hydroxytyrosol; **MCF:** Michigan Cancer Foundation; **PAHs**: Polycyclic aromatic hydrocarbons; **PC:** Prostate cancer; **PTEN:** Phosphatase and tensin homolog; **ROS:** Reactive oxygen species; **TRPV1:** Transient receptor potential cation channel subfamily V member 1; **TRPV6:** Transient Receptor Potential

Cation Channel Subfamily V Member; **US$:** United States dollar; **WHO:** World Health Organization; **WWP1:** WW Domain Containing E3 Ubiquitin Protein Ligase 1.

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