

THE IMPORTANCE OF BIOLOGICALLY ACTIVE COMPOUNDS OF HOP (*HUMULUS LUPULUS*) IN PHARMACEUTICAL USE INCREASE IMPACT OF HOP INDUSTRY IN THE PERFORMANCES OF US ECONOMY

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Abstract: This article is focusing on numerous health-promoting effects of hop ranging from antioxidative, sedative, and anti-inflammatory potentials, over anticarcinogenic features to estrogenic activity. Because of the greatly differences in the structure and properties of the hop natural compounds, there have been developed a wide range of methods for their isolation and chemical analysis, as well as for determining their antioxidative, antimicrobial and antigenotoxic potentials. Even if hop remain the principal ingredient for providing the taste, stability and antimicrobial protection of beer, researchers found applications in the pharmaceutical and other food industries as well, therefore, hop should be more exploited for healing and prevention of several diseases, as the population is more demanding for natural cures with less side effects. The increase of pharmaceutical demands over hop production is impacting US hop industry. As is well known, hop industry is playing an important role in the US economy. We analyze the production of hop in US during the period 1947-2018.

Keywords: biologically active compounds of hop, bitter acids, essential oils, hop industry, hops polyphenols.

Background

The use of hop as a medicinal plant has more than 2000 y of history (Koetter and Biendl, 2010). The ancient healers used hop against leprosy, foot odour, constipation, and for blood purification (Karabin *et al.*, 2015).

The use of hop in General Health is because of his Antioxidant properties of Polyphenols, of essential oils and of the bitter acids.

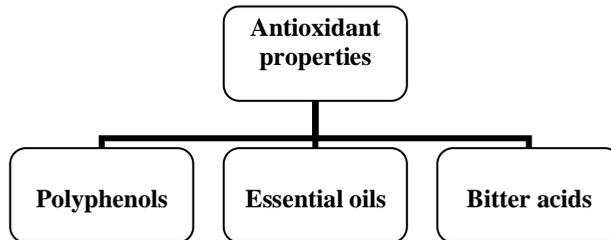


Figure 1. Antioxidant properties of HOP (authors projections)

The polyphenols have an antimicrobial activity which is based on inhibiting the replication of microorganisms. Some of these microorganisms are bacteria, fungi, and protozoan parasites. The same mechanism was observed against factors that induce various DNA or RNA viruses. The mechanism of antimicrobial activities of polyphenols involves the ability to penetrate phospholipid cell membranes and cause inhibition or to accumulate inside cells (Alvesalo *et al.*, 2006).

In general, extracts that contain hop essential oils usually have weaker antimicrobial activity than extracts. Products that are based hop oil, showed moderate antibacterial effects against the Gram-positive bacteria *Bacillus*, Gram-negative bacteria *E. coli*, *subtilis* and *S. aureus*. Also this kind of products showed an antifungal activity against the fungus *Trichophyton interdigital*, and the yeast *Candida albicans* (Langezaal *et al.*, 1992). This experiment was also confirmed by Jirovetz *et al.* (2006) who demonstrated antimicrobial effects of hop oils against *Enterococcus faecalis* and Gram-positive *S. aureus*, *Salmonella* sp. and Gram-negative *Escherichia coli*, and also over the yeast *C. albicans*. In this study, was also demonstrated that the properties of selected pure terpenes were examined. Some of terpenes' compounds inhibited growth of *P. aeruginosa* and Gram-negative *Proteus vulgaris*.

Beer is considered to be a 'functional beverage'. Some of these reasons are its absence of microbial contamination and its prolonged shelf-life (Zanoli and Zavatti, 2008; Van Cleemput *et al.*, 2009).

The use of hops in beer creates a mechanism of microbial inhibition of beer spoilage bacteria (Gram-positive bacterial species such as *Lactobacillus*, *Streptococcus*, *Staphylococcus*, *Micrococcus*, *Bacillus*, and *Pediococcus*) was studied by Zanoli and Zavatti (2008). Van Cleemput *et al.*

(2009), and it is also is encouraged to be used in other food processing industries and to be studied his effects in other food products.

Some studies conclude that Humulinic acids may be used in food preservation. This type of acids does not impart any bitter taste. Because of these characteristics as taste-neutral food preservatives of Humulinic acids, they may have future potential to be used in food processing industries.

Hop compounds can also be used in human or veterinary medicine, because of their antibacterial effects. Researchers have also reported good results for combination of antibiotics and hop compounds (Natarajan *et al.*, 2008).

Hops production is concentrated in moist temperate climates, with much of the world's production occurring near the 48th parallel north. Hop plants prefer the same soils as potatoes and the leading potato-growing states in the United States are also major hops-producing areas.

Table 1

Biggest hop production (tonnes)

Country	Hop production in tonnes
United States	44324
Germany	39000
Czech Republic	6100
China	4500
Poland	2826
Slovenia	2600
UK/England	1400
Australia	1200
Spain	950
New Zealand	760
Argentina	200

(Source: https://en.wikipedia.org/wiki/Hops#cite_note-23)

We see an opportunity to evaluate the impact of HOP industry in US economy in the circumstances of the new trend by the fact that natural remedies and treatments are more and more used by people.

Taking in consideration that hop cones contain many biologically active phenolic compounds and other important compounds have attracted the attention of many phytopharmaceutical companies. That is why there have been many studies about hop cone and alpha acid production in the world. The most important fraction of hop resins is the α -bitter acids. The

lupulin glands of hop cones secreted them in the form of a yellow powder (Okada and Ito, 2001).

However, because of their valuable compounds, they are in the forefront for many potential biomedical applications.

Table 2

Dynamics of the surfaces and hop production in the world, alpha acid productions and beer productions during 2001-2012

Year	Hop surface (ha)	Hop cone production (mt)	Yield (t/ha)	Alpha acid production (mt)	Alpha acid (g/hl of beer)	Beer production (million hl)
2001	58,903	99,214	1.68	8,646	5.4	1,424
2002	56,237	100,932	1.79	8,749	5.3	1,443
2003	53,500	87,056	1.63	6,722	5.2	1,479
2004	50,639	92,266	1.82	8,103	5.1	1,552
2005	50,273	94,385	1.88	7,903	5	1,603
2006	49,466	85,585	1.73	7,103	4.9	1,696
2007	50,455	91,584	1.82	7,663	4.8	1,787
2008	57,297	111,175	1.94	10,424	4.6	1,819
2009	56,787	113,669	2	10,952	4.3	1,833
2010	52,029	99,899	1.92	9,477	4.2	1,863
2011	48,529	100,604	2.07	10,378	4.2	1,929
2012	46,971	89,090	1.9	9,139	4.3	1,951

(Source: Cernea, 2013)

In the below analyses we are using some statistical tools similar to those used to analyse other American industries in correlation with GDP (Pop *et al.*, 2017) or dynamic of Romanian economy.

Based on the sample data, regression models are developed. Several models are available in the software package. The logic behind the models designed, is based on the natural behaviour and correlation of the variables (Okada and Ito, 2001).

General Health-Promoting Effects, sample data and preliminary analysis

General Health-Promoting Effects

Natural remedies and treatments where we can use the hop most important fractions are: obesity and diabetes, insomnia, neurodegenerative diseases such as dementia, Alzheimer's disease, Parkinson's disease, cancer,

prevention of osteoporosis and protection of bone health, cardiovascular diseases, and menopausal symptoms such as osteoporosis, hot flushes, night sweats and insomnia.

Studies of the sedative effects of hops

Besides the sedative effects of beer because of his ethanol compound, was also demonstrated the ability of hop compounds to affect the central nervous system. During lots of years were studies on the sedative properties of hops that were based on observations over workers during harvesting and processing of hop cones .They were developing symptoms of sleepiness and fatigue (Koetter and Biendl, 2010). These sedative effects of ethanol from hop resin and CO₂ hop extracts were also tested by Schiller *et al.* (2006). In his work, higher doses (up to 500 mg/kg b.w.) were used to test the resins impact and essential oil components on locomotors activity, sleeping time induced by ketamine, and mice body temperature. The most important sedative components of hops were shown to be α -bitter acids. Beside this compound was also demonstrated that a big contribution was β -bitter acids and essential oils.

Many times, hops are combined with another herb in medicinal products. These herbs are having hypnotic properties and anxiolytic. One of these plants is valerian, *Valeriana officinalis* L. (Bone and Mills, 2012). Different combinations of hops and valerian are already available for buying as soothing preparations in the form of baths or drops (Weeks, 2009). A study demonstrated that the use of a combination of hops and valerian extracts will improve the quality of sleep. And also showed that can reduce the required high doses of others pharmaceuticals used in the treatment of insomnia. This study was a double-blind placebo-controlled by Muller and others (Müller-Limmroth and Ehrenstein, 1977).

There are studies that showed the interesting aspect of nonalcoholic beer that has also these sedative effects, even that the most source of hop compounds in the human diet is beer. The study made by Franco *et al.* (2012) demonstrated that moderate consumption of non-alcoholic beer can improve the quality of sleep. There were studies of different subjects who were involved in stressful activities that cause significant fluctuations in the natural sleep rhythm. One of these stressful activities is considered to be a nurse.

Neurobiological-Related Activities

Different epidemiological studies will show a decreased risk of various neurodegenerative diseases. In these studies, was used high dietary

intake of polyphenols on different subjects. Some of these neurodegenerative diseases are: Alzheimer's disease, dementia (50% reduction), or Parkinson's disease. Xanthohumol was also demonstrated to exhibit neuroprotective activity. This activity was demonstrated against ischemic stroke in rats.

Xanthohumol has been characterized a cancer chromoprotective agent in *in vitro* studies, while other prenylated compounds are potent phytoestrogen know to date.

Cancer-related activities

In industrialized countries the leading causes of death is cancer. The demand of cancer treatments in terms of time and financial requirements, instrumentation, and psychological is increasing rapidly. Therefore, of this major importance, a significant number of scientific studies are focused on substances with anticarcinogenic potential. Numerous studies made in the last part of this century have demonstrated the anticarcinogenic potential of polyphenols. There was also showed that polyphenols have the ability to stop and reverse the process of tumour formation. They will exhibit a protective effect against the formation and development of cancer. These studies were conducted by Gerhauser on different models *in vitro* and *in vivo*.

Estrogenic and Osteoporosis-Related Activities

In 1953 was the 1st time mentioned that hops can have estrogenic properties. Hops have been also considered to have the ability to bind to estrogen receptors (subtypes ER α and ER β), and the ability to inhibit specific enzymes or to mimic estrogenic actions, because of the important source of substances having estrogenic effects. The intake of prenylflavonoids is associated with the prevention of osteoporosis, whereas prenylflavonoids can modulate bone cell expression, increasing the osteoblasts (cells responsible for bone formation) and decreasing the osteoclasts (bone cells that resorb bone tissue). The estrogenic compounds from hop raisin made from hop possible alternative to hormone replacement therapy (HRT) Because of this, hop flavonoids can be used to treat menopausal symptoms such as hot flushes, osteoporosis, insomnia and night sweats. Treating these disorders with HRT is related to an increased risk of breast or endometrial cancer.

Obesity and Diabetes-Related Activities

In the last century in the western countries, the metabolic diseases have reached epidemic proportions. These are caused by the cardiovascular complications and mortality. The metabolic syndrome is associated with risk from 5 factors. These factors are abdominal (central) obesity, elevated blood pressure, elevated plasma glucose, high serum triglycerides, and low high-density lipoprotein levels. Treatments that were developed are focused on reduction of the risk of heart disease by lowering LDL cholesterol. These treatments also include reducing high blood pressure followed by the treatment of diabetes. A very important aspect is the reduction of weight following proper diet and exercise (Dillard and German, 2000; Miranda *et al.*, 2005).

Cardiovascular-Related Activities

There are studies that showed that polyphenols have an antioxidant potential. They can prevent the oxidation of LDL induced by metal ions (copper and iron) or by tert-butyl hydroperoxide. They can also improve lipid profiles. However, it was demonstrated that polyphenolic substances are able to enhance the concentration of HDL cholesterol in plasma (Chen and Blumberg, 2009).

Sample data and preliminary analysis

In case of HOP industries we used data since 1866 and in case of GDP (Gross domestic product is a monetary measure of the market value of all the final goods and services produced in a specific time period) we are using data since 1960. This long period of time covers several cycles of economic growth and crisis. Thus, our analyses have a high probability of modelling the reality in a reliable manner and our conclusions have a solid base.

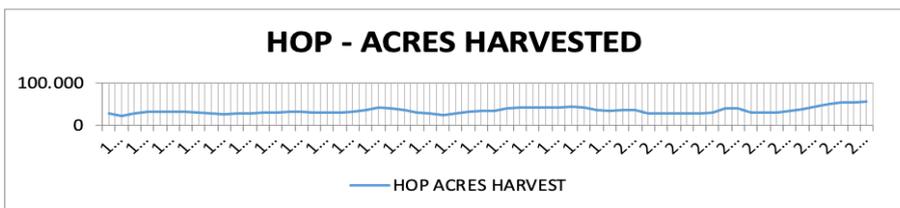


Figure 2. Hop – harvested acres during 1960 - 2018
(authors projections)

Data regarding figure 2 are based on data provided from one source. Data corresponding to the period 1960 to 2018 are obtained from the United States Department of Agriculture (USDA, 2020).

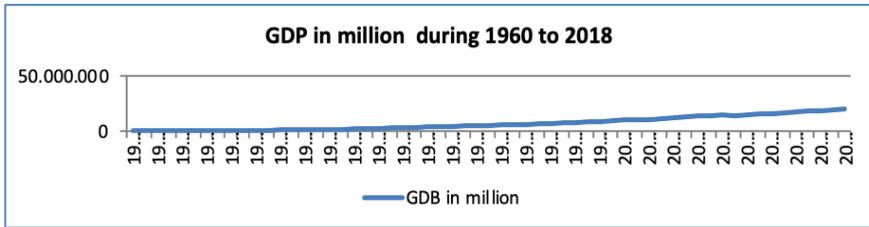


Figure 3. GDP in million during 1960 - 2018 (authors projections)

Data regarding figure 3 are based on data provided from two sources. Data corresponding to the period 1960 to 2018 are obtained from the World Bank (2020) and US Department of Commerce, Bureau of Economic Analysis (2020).

To evaluate the performances of US economy we chose to use data regarding GDP and HOP – harvested acres during the period from 1960 to 2018.

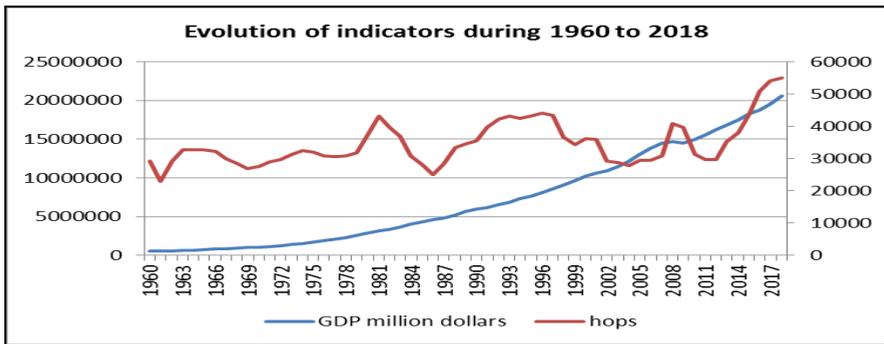


Figure 4. GDP vs. HOP harvested (authors projections)

Starting from the representation of this series of data we built the linear function which covers the evolution of both parameters in the past 58 years.

Regression models

In this section we will develop some regression models used to understand and explain the correlations between HOP – harvested acres and GDP during the last 59 years.

Evolution in time of hop – acres harvested

Analysing data provided by the United States Department of Agriculture, corresponding to the last 58 years, the following time series is generated:

$$\text{hops} = 28508.2 + 202.258 * \text{time}$$

According to this time series analysis, surface of hops harvested is increasing with 202.258 acres per year.

The following table is presenting predictions and prediction limits (with 95% confidence level) for hop - acres harvested. Values are determined using the above-mentioned time series.

Table 3

Prediction for hop acres harvested

Time period	Predicted hop acres harvested	Prediction interval for hop acres harvested (95% confidence level)
2019	40643.7	28295.4 – 52992.0
2020	40846.0	28477.1 – 53214.8
2021	41048.2	28658.2 – 53438.3

(authors projections)

Evolution in time of GDP

Analysing based on the model (Pop and Luca, 2003) present in the literature; the data provided by the United States Department of Agriculture, corresponding to the last 59 years, the following time series is generated:

$$\text{GDP} = -3.06294E6 + 342737 * \text{time}$$

According to this time series analysis, GDP is increasing with 342.737 million dollars per year.

The following table is presenting predictions and prediction limits (with 95% confidence level) for GDP. Values are determined using the above-mentioned time series.

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Table 4

Prediction for GDP		
Time period	Predicted GDP	Prediction interval for GDP (95% confidence level)
2019	17.501.300	14.306.000 – 20.696.600
2020	17.844.000	14.643.400 – 21.044.600
2021	18.186.700	14.980.600 – 21.392.900

(authors projections)

Correlation between GDP and hop – acres harvested

Linear and polynomial regressions are employed to study the correlation between the two variables.

The linear regression, determined using Statgraphics software generates the following model:

$$hops = 30519.2 + 0.000561946 * GDP$$

According to this model, an increase of GDP with 10 billion dollars, determines an increase with 5.6 acres for the surface of hop – harvested.

The above-mentioned regression model is representative with a 95% confidence level. Thus, we might estimate the trend for surface of hop according to the evolution of GDP.

Table 5

Prediction for hop – acres harvested based on GDP

GDP	Predicted hop acres harvested	Prediction interval for hop acres harvested (95% confidence level)
20.696.600	42149.6	29548.5 - 54750.6
21.044.600	42345.1	29718.8 - 54971.5
21.392.900	42540.9	29888.6 - 55193.1

(authors projections)

The polynomial regression is constructed to identify which part from the variation of hop-acres harvested is due to variation of GDP.

The regression model is presented in figure 5.

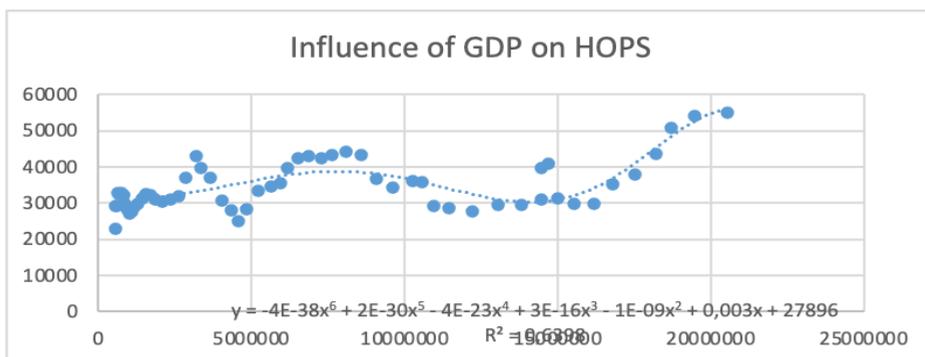


Figure 5. Polynomial regression for GDP and hop - acres harvested (authors projections)

In case of the data series regarding HOP – ACRES HARVESTED the linear function that came along is as follow:

$$\text{Hops} = -4\text{E}-38*\text{GDP}^6 + 2\text{E}-30\text{GDP}^5 - 4\text{E}-23 \text{GDP}^4 + 3\text{E}-16 \text{GDP}^3 - 1\text{E}-09 \text{GDP}^2 + 0.003 \text{GDP} + 27896$$

According to this model, the determination coefficient is 0.6398, which indicates that 63.98% from the variation of hop-acres harvested is due to variation of GDP.

Conclusions

Hop also contains the compounds with less importance in brewing. Prenylated flavonoids are one of these examples. This is the reason why there are recently efforts and studies for genetic manipulation and breeding of hop. The goal is to the increase levels of the biologically active compounds. These compounds can be used for pharmaceutical purposes. The 1st variety used for pharmaceutical purposes was variety VITAL bred by Hop Research Institute in Saaz. VITAL was bred in 2008 and it is especially important because it has a high content of desmethyl-xanthohumol. This active compound is a direct precursor of 8-prenylningenin. Other promising substances are prenylated chalcones and especially xanthohumol, which has been identified as a substance with a big potential in cancer treatments. This compound induces apoptosis of cancer cells, modulates biotransformation of carcinogens, and inhibits angiogenesis. Over the last decade have been introduced on the market several dietary supplements based on hops. Through some fundamental

clinical trials conducted by van Breemen were confirmed the effects of some food supplements.

The increase of pharmaceutical demands over hop production and in what kind of varieties of hops would be harvested it is affecting US hop industry. Therefore, we created a tool to help with the prediction for next year of harvesting.

According to the models, we were able to predict the values and the prediction limits for the period 2019 – 2021.

Prediction limits for 2020 (with a 95% confidence) in case of HOP – ACRES HARVESTED, determined using time series are 28477.1 – 53214.8, while those determined using linear regression are 29888.6 - 55193.1.

Models analysed emphasize the possibility to model evolution of hop sector of activity using statistical tools. Being able to predict the total amount of acres harvest we can predict the value of production, taking from there we can predict the volume that stand for sale.

Prediction limits for 2020 (with a 95% confidence) in case of GDP, determined using time series are 14.643.400 – 21.044.600.

Also, in this case the tool we have built can be used to predict the evolution of GDP, which show us the evolution of the US economy. Having this kind of data, the public, the economists, the analysts, the researchers and all who can be interested in can use it to make prediction and built scenarios capable to predict evolution of businesses, sectors of industries and the whole economy.

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