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Optimization of the hierarchical supply chain in the pharmaceutical industry

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Abstract: This paper discusses the modeling and solution of a hierarchical supply chain problem in the pharmaceutical industry. The considered supply chain includes the levels of suppliers, production centers, and distribution, which are taken into account in the decisions of the location of capacity facilities, optimal allocation of flow, and vehicle routing at the same time. Due to the indeterminacy of the problem environment, the two-stage probabilistic programming method has been used to control the model, and the new WOGA algorithm has been used to solve the problem. The presented algorithm is a combination of the Whale Optimization Algorithm (WOA) and Genetic Algorithm (GA) algorithms, which are used to minimize the costs of the entire designed network. The results obtained from the model analysis show that WOGA has a high efficiency in solving the developed mathematical model compared to GA and WOA. There was no significant difference between the averages of the objective function and the computational time between different solution methods. Since the perishability of the drug in transportation was considered in this article, it was observed that the cost of the entire network reaches its highest level if the period of perishability is 1. Because the production and distribution centers cannot have inventory in their warehouses and must meet the demand of pharmacies in every period.

Keywords: *Hierarchical supply chain, Pharmaceutical industry, Two-level probabilistic planning, WOGA.*

1. Introduction

The pharmaceutical industry is one of the most important fields in any country and is defined as a system consisting of processes, operations, and organizations involved in the discovery, development, and production of drugs and medicines. In the meantime, the supply chain for treatment is one of the most important strategic issues in the pharmaceutical and healthcare industries [1]. The drug supply chain is the path through which the right quality drug products are distributed to end-users at the right place and time [2]. In the past, pharmaceutical companies ignored the concept of drug supply chain management, but currently, several factors are driving pharmaceutical companies to change their conventional business methods, one of which is the supply chain, and it is becoming a competitive advantage. One of the most important competitive advantages that can be presented in this field is the ability to solve and cover the pharmaceutical needs of society with the greatest speed, accuracy, and cost [3]. Therefore, the criteria of production and logistics management, financial ability, knowledge and technology management, marketability, and inter-organizational and industrial competition have been considered in this field. Most of the research that has been done in the field of drug supply chains is in the field of laws related to safety and effectiveness. The main planning issue has rarely been addressed in drug supply chain issues. The main task of the main planning is to determine the amount of supply,

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production, and distribution of facilities at different levels of the supply chain in a medium-term period [4].

A hierarchical supply chain is usually considered an integrated process of a group of organizations, such as suppliers, manufacturers, distributors, and retailers, working together to cover and support raw materials for final products and their distribution to end customers. Supply chain network design is one of the key decision-making issues in supply chain management, which plays a very important role in supply chain performance [5]. The pharmaceutical industry, considered a significant global industry, can be defined as a complex set of processes, operations, and organizations involved in drug discovery, development, and manufacture [6].

Despite all the advances and improvements in manufacturing, storage, and distribution methods, pharmaceutical companies are still significantly far from being effective in satisfying market demand and paying huge costs for drug supply. In this way, the supply, production, storage, and transfer of medicine between suppliers, factories, and pharmacies require careful management [7]. Failure to pay attention to the perishability of the drug and also the lack of proper design of the transportation network causes a lot of financial losses on the one hand and, on the other hand, causes loss of life due to the patient or customer not receiving the drug. Since the above criteria have many unpredictable factors, special planning models should be used to solve this problem [8]. Considering the very heavy costs of the pharmaceutical industry and the need for proper planning in long-term and mid-term decisions, this has led to the design of a suitable mathematical model with the stated cases and its implementation in the pharmaceutical industry. The complexity of mathematical programming combined with the location of the optimal allocation of the flow of drugs from producers to demand centers and vehicle routing makes it necessary to use the tools of meta-initiative methods to solve the problem.

In this paper, the problem of a hierarchical supply chain in the pharmaceutical industry has been investigated. The utilization of two-stage probabilistic planning method has been employed in order to manage the model, taking into account the uncertainties associated with demand, transportation, and maintenance expenses. Also, simultaneous decisions such as location-routing-allocation have led to the NP-Hard problem, which is used to solve the model of a new hybrid algorithm called WOGA (a combination of the Whale Optimization Algorithm (WOA) and the Genetic Algorithm (GA)).

The article's structure is as follows: the research literature review and the research gap investigation have been discussed in the second part. In the third part, the mathematical model is presented in the problem of the hierarchical supply chain in the pharmaceutical industry, and the two-stage probabilistic programming method is used for modeling. The fourth part discusses the WOGA method and initial solution design. The fifth part concerns the analysis of different numerical examples and the model's validation. Finally, conclusions and future work solutions are presented for the sixth section.

2. Literature Review

A hierarchical supply chain is ordinarily considered an integrated handle of organizations, such as providers, producers, wholesalers, and retailers, that work together to cover and back crude materials to conclusion items and their dispersion to conclusion clients. In the meantime, the significance of the progressive supply chain within the pharmaceutical industry has drawn the attention of numerous analysts. Nozari, et al. [9] addressed the simultaneous optimization of development strategy, product introduction, and investment in a pharmaceutical system. Najafi, et al. [10] optimized a pharmaceutical company's worldwide supply chain to demonstrate and examine distinctive generation and dissemination costs and assess rates. Szmelter-Jarosz, et al. [11] centered on recognizing critical on-screen characters within the drug supply chain that will alter biopharmaceuticals' buying, conveyance, and dealing. Nozari, et al. [9] modeled the nature of uncertainty in the amount and quality of drugs delivered within the plan of the supply chain organization. Nozari, et al. [9] model the pharmaceutical supply chain arrangement issue. They inspected different key choices, such as building up generation and dissemination centers, and strategic choices, such as the ideal assignment of fabric stream. Nozari,

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et al. [9] explored a three-level show of the medical supply chain organization and illuminated the demonstration utilizing the optimization recreation strategy. Szmelter-Jarosz, et al. [11] utilized a heuristic approach to unravel a sedate supply chain demonstrated in perishability mode. Jamil, et al. [12] conducted an overview of various blockchain-based tracking solutions for the pharmaceutical industry. They analyzed how blockchain tracking solutions affect the visibility of multiple networks of supply chain distribution designs.

Zandkarimkhani, et al. [13] defined a bi-objective blended-numbers direct programming demonstrated for planning a perishable pharmaceutical supply chain organized beneath request instability. The destinations of the proposed demonstration were to; at the same time minimize, the whole toll of the organization and the sum of misplaced requests. They utilized fluffy programming to unravel the show. Goodarzian, et al. [14] displayed a multi-objective model for medicating supply chain systems based on a fuzzy robust method and compared meta-heuristic calculations in it. Nasrollahi and Razmi [15] modeled a four-layer, multi-period supply chain, counting manufacturers, distribution centers, hospitals, and patients. For this, they solved a multi-objective model, including demand coverage and cost minimization, using MOPSO (Multi-Objective Particle Swarm Optimization) and NSGA II (Non-Dominated Sorting Genetic Algorithm II).Goodarzian, et al. [16] proposed a new multi-objective optimization approach for pharmaceutical supply chain design problems to minimize pharmaceutical products' total cost and delivery time to hospitals and pharmacies and maximize reliability. Delfani, et al. [17] utilized the fuzzy robust optimization strategy to demonstrate the progressive supply chain issue within the pharmaceutical industry beneath vulnerability. In this demonstration, they considered turnaround time and unwavering quality as non-deterministic parameters. Shakouhi, et al. [18] examined two pharmaceutical supply chains beneath the item life cycle and marketing methodologies. This study included a multi-objective mixed-integer nonlinear programming model. Ishizaka, et al. [19] selected suppliers in a closed-loop drug supply chain using the BWM-GAIA method (best–worst method and geometrical analysis for interactive aid). They evaluated suppliers' performance using BWM. Ahmad, et al. [20] developed sustainability objectives in the pharmaceutical supply chain optimization framework with various constraints under uncertainty. They ranked different sets of problem solutions using TOPSIS. Sindhwani, et al. [21] centered on moderating the impacts of COVID-19 widespread in India's pharmaceutical dissemination organization. They have gotten the finest sedate distribution location utilizing stochastic optimization and Lagrange discharge.

The literature review shows that no comprehensive model of the hierarchical supply chain network in the pharmaceutical industry can make location-allocation-routing decisions simultaneously. Also, combined solution methods are not seen in the subject literature. Therefore, the presentation of the combined algorithm in this article for the designed model is considered one of the innovations of the paper.

3. Definition of the Problem

In this paper, a hierarchical supply chain model for the pharmaceutical industry has been presented. Figure 1 shows the supply chain levels in the pharmaceutical industry and includes a set of suppliers $j = \{1, \dots, J\}$, production centers $k = \{1, \dots, K\}$, distribution centers $l = \{1, \dots, L\}$ and pharmacies are $m, c = \{1, \dots, C\}$. In this hierarchical supply chain, suppliers supply raw materials needed to produce different drugs $p = \{1, \dots, P\}$ in different periods $t = \{1, \dots, T\}$ with heterogeneous vehicles $v = \{1, \dots, V\}$ with different capacities are sent to the production centers. After storing the raw materials and producing drugs according to the needs of the pharmacies, the production centers send them to the distribution centers for distribution. Due to the perishability of the drug, the distribution centers are responsible for the storage of the drug or the immediate distribution to the pharmacies. Due to the existence of a time window for each pharmacy, the distribution centers determine the best route for the distribution of drugs to pharmacies. This distribution takes the form of vehicle routing. If the

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distribution centers do not distribute the drugs at the time each pharmacy specifies, the network costs will increase to cover the penalty. In the model presented in this article, drugs have a limited life and must be delivered to pharmacies before they become perishable. Due to the uncertainty in the amount of drug demand by each pharmacy and its effect on the number of drug products that can increase the costs of the hierarchical supply chain, this amount of demand has been considered in different scenarios $s = \{1, \ldots, S\}$.

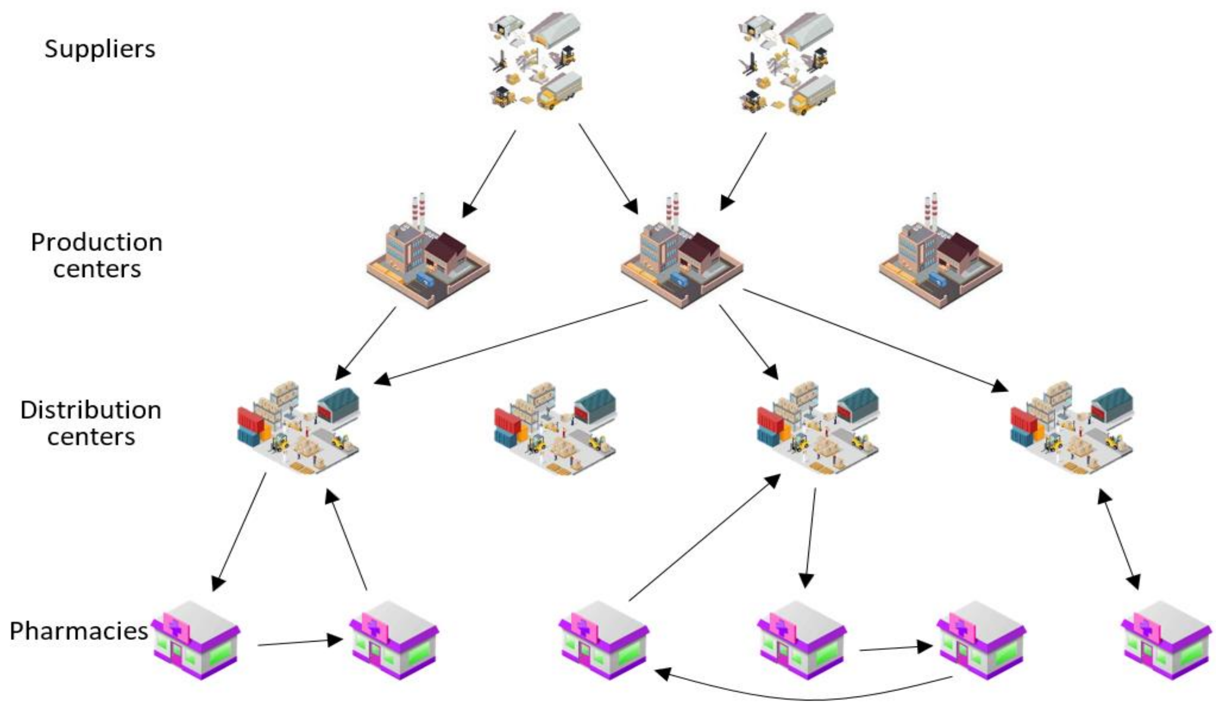

Figure 1.
Hierarchical supply chain for the pharmaceutical industry.

In the model presented in this article, we will only use some of the suppliers, production centers, and distribution centers to optimize the costs of the hierarchical supply chain network for the pharmaceutical industry. Therefore, according to the amount of demand and the conditions governing the problem, determining the number of centers mentioned for establishment is among the strategic decisions of the problem. On the other hand, once the centers are chosen, other tactical decisions include the best way to divide the flow between the supplier and the production center, the production center and the distribuition center, and the best way for drugs to get from the distribution centers to pharmacies. Therefore, the proposed model combines the three NP-hard problems of capacity facility location, optimal flow allocation, and vehicle routing. The following assumptions are considered for modeling the problem:

- The demand from pharmacies for different drugs should be estimated.
- Transportation costs, drug storage costs, and demand in different scenarios have different values.
- The location and number of suppliers, production centers, and distribution centers are unclear.
- The capacity of vehicles to distribute medicines is known.
- Each pharmacy has a time window during which the center's request must be answered.
- Each scenario has a different probability of occurrence.

According to the stated assumptions, the main goal of this research is to reduce the costs of the entire supply chain network, and a two-level programming method has been used to control the non-deterministic model. Based on the assumptions stated below, the symbols used in the modeling are shown.

3.1. Parameters

E_j	Fixed cost of supplier selection at location j
H_k	The fixed cost of choosing a production center at location k
U_l	The fixed cost of choosing a distribution center at location l
F_v	The fixed cost of using the vehicle v
$\tilde{t}_{jks}$	Transportation cost of each drug unit between supplier j and production center k in scenario s
$\tilde{t}_{kls}$	Transportation cost of each drug unit between production center k and distribution center l in scenario s
$\tilde{t}_{lcs}$	Transportation cost of each product unit between distribution center l and pharmacy c in scenario s $l, c \in L \cup C$
$\tilde{h}_{ks}$	The cost of keeping each unit of medicine in production center k in scenario s
$\tilde{h}'_{ls}$	The cost of keeping each unit of medicine in the distribution center l in scenario s
θ	Penalty fee for exceeding the time window
c_l	The cost of distributing each unit of medicine by the distribution center l
t'_{lc}	The time of drug transfer by vehicle between distribution center l and pharmacy c $l, c \in L \cup C$
$[a_c, b_c]$	Time window of pharmacy c to receive medicine
$\tilde{d}_{cpts}$	Pharmacy c's demand for drug p in time period t
u_p	Perishability time of drug p
ca_{jp}	The maximum capacity of supplier j to supply drug p
ca_{kp}	The maximum capacity of production center k of drug production p
ca_{lp}	The maximum capacity of the distribution center l of drug distribution p
ca_v	Vehicle capacity v
p_s	The probability of occurrence of scenario s

3.2. Decision Variables

Y_{jkpts}	The volume of drug transfer p between supplier j and production center k in time period t in scenario s
W_{klpts}	The volume of drug transfer p between production center k and distribution center l in time period t in scenario s
V'_{lpts}	The total volume of drug transport p by distribution center l in time period t in scenario s
T_{klptrs}	The volume of drug transfer p between production center k and distribution center l in time period t and produced in time period r in scenario s
Q_{kptrs}	Inventory of drug p in production center k in time period t and produced in time period r in scenario s
Q'_{lptrs}	Inventory of drug p in distribution center l in time period t and produced in time period r in scenario s
Z_j	If the supplier is selected in location j, it takes the value 1 and otherwise 0.
Z_k	If the production center is selected at location k, it takes the value 1 and otherwise 0.
Z_l	If the center of the distribution is selected at location l, it takes the value 1 and otherwise 0.
Z_v	If vehicle v is selected, it takes the value 1 and otherwise 0.

I_{lcts}	If the pharmacy c is assigned to the distribution center l in the time period t in the scenario s, it takes the value 1 and otherwise 0.
Z_{lcvts}	If pharmacy c is visited after distribution center l by vehicle v in time period t and in scenario s, it takes the value 1 and otherwise 0. $l, c \in L \cup C$.
U_{cvts}	Auxiliary variable for sub-tour deletion constraint.
D_{lcvts}	The arrival time of vehicle v assigned to distribution center$l$ in visiting pharmacy c in time period t in scenario s.
DT_{cvts}	The value of exceeding the time window in the arrival of vehicle v to pharmacy c in time period t in scenario s.

According to the defined symbols, the hierarchical supply chain model for the pharmaceutical industry as a mixed integer linear mathematical programming model will be as follows:

$$Min \sum_{j=1}^{J} E_j Z_j + \sum_{k=1}^{K} H_k Z_k + \sum_{l=1}^{L} U_l Z_L + \sum_{v=1}^{V} F_v Z_v + \sum_{k=1}^{K}\sum_{p=1}^{P}\sum_{t=1}^{T}\sum_{r=1}^{t}\sum_{s=1}^{S} p_s \tilde{h}_{ks} Q_{kptr} + \sum_{l=1}^{L}\sum_{p=1}^{P}\sum_{t=1}^{T}\sum_{r=1}^{t}\sum_{s=1}^{S} p_s \tilde{h}'_{ls} Q'_{lptr} + \sum_{j=1}^{J}\sum_{k=1}^{K}\sum_{p=1}^{P}\sum_{t=1}^{T}\sum_{s=1}^{S} p_s \tilde{t}_{jks} Y_{jkpts} + \sum_{k=1}^{K}\sum_{l=1}^{L}\sum_{p=1}^{P}\sum_{t=1}^{T}\sum_{s=1}^{S} p_s \tilde{t}_{kls} W_{klpt} + \sum_{l=1}^{L\cup C}\sum_{c=1}^{L\cup C}\sum_{v=1}^{V}\sum_{t=1}^{T}\sum_{s=1}^{S} p_s \tilde{t}_{lcs} Z_{lcvts} + \sum_{l=1}^{L}\sum_{p=1}^{P}\sum_{t=1}^{T}\sum_{s=1}^{S} p_s c_l V'_{lpts} + \sum_{c=1}^{C}\sum_{v=1}^{V}\sum_{t=1}^{T}\sum_{s=1}^{S} p_s \theta DT_{cvts} \quad (1)$$

$s.t.$:

$$\sum_{r=1}^{t} Q_{kptrs} = \sum_{j=1}^{J} Y_{jkpts} - \sum_{l=1}^{L} W_{klpts}, \quad \forall k, p, t = 1 < u_p, s \quad (2)$$

$$\sum_{r=1}^{t} Q_{kptrs} = \sum_{r=1}^{t-1} Q_{kpt-1rs} + \sum_{j=1}^{J} Y_{jkpts} - \sum_{l=1}^{L} W_{klpts}, \quad \forall k, p, 1 < t < u_p, s \quad (3)$$

$$\sum_{r=t+1-u_p}^{t} Q_{kptrs} = \sum_{r=t+1-u_p}^{t-1} Q_{kpt-1rs} + \sum_{j=1}^{J} Y_{jkpts} - \sum_{l=1}^{L} W_{klpts}, \quad \forall k, p, t \geq u_p, s \quad (4)$$

$$W_{klpts} = \sum_{r=1}^{t} T_{klptrs}, \quad \forall k, l, p, t < u_p, s \quad (5)$$

$$W_{klpts} = \sum_{r=t+1-u_p}^{t} T_{klptrs}, \quad \forall k, l, p, t \geq u_p, s \quad (6)$$

$$Q_{kptrs} = \sum_{j=1}^{J} Y_{jkpts} - \sum_{l=1}^{L} T_{klptrs}, \quad \forall k, p, t = r, s \quad (7)$$

$$Q_{kptrs} = Q_{kpt-1rs} - \sum_{l=1}^{L} T_{klptrs}, \quad \forall k, p, t - r < u_p, s \quad (8)$$

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$$\sum_{r=1}^{t} Q'_{lptrs} = \sum_{k=1}^{K} W_{klpts} - V'_{lpts}, \quad \forall l, p, t = 1 < u_p, s \tag{9}$$

$$\sum_{r=1}^{t} Q'_{lptrs} = \sum_{r=1}^{t-1} Q'_{lpt-1rs} + \sum_{k=1}^{K} W_{klpts} - V'_{lpts}, \quad \forall l, p, 1 < t < u_p, s \tag{10}$$

$$\sum_{r=t-u_p+1}^{t} Q'_{lptrs} = \sum_{r=t-u_p+1}^{t-1} Q'_{lpt-1rs} + \sum_{k=1}^{K} W_{klpts} - V'_{lpts}, \quad \forall l, p, t \geq u_p, s \tag{11}$$

$$V'_{lpts} = \sum_{r=1}^{t} \sum_{c=1}^{C} B_{lcptrs}, \quad \forall l, c, p, t < u_p, s \tag{12}$$

$$V'_{lpts} = \sum_{r=t-u_p+1}^{t} \sum_{c=1}^{C} B_{lcptrs}, \quad \forall l, c, p, t \geq u_p, s \tag{13}$$

$$Q'_{lptrs} = \sum_{k=1}^{K} T_{klptrs} - \sum_{c=1}^{C} B_{lcptrs}, \quad \forall l, p, t = r, s \tag{14}$$

$$Q'_{lptrs} = Q'_{lpt-1rs} - \sum_{c=1}^{C} B_{lcptrs}, \quad \forall l, p, t - r < u_p, s \tag{15}$$

$$\sum_{k=1}^{K} Y_{jkpts} \leq ca_{jp} Z_j, \quad \forall j, p, t, s \tag{16}$$

$$\sum_{k=1}^{K} W_{klpts} \leq ca_{lp} Z_l, \quad \forall l, p, t, s \tag{17}$$

$$\sum_{j=1}^{J} Y_{jkpts} \leq ca_{kp} Z_k, \quad \forall k, p, t, s \tag{18}$$

$$V'_{lpts} = \sum_{c=1}^{C} \tilde{d}_{cpts} Z_{lcts}, \quad \forall l, p, t, s \tag{19}$$

$$\sum_{v=1}^{V} \sum_{l=1}^{C \cup L} Z_{lcvts} = 1, \quad \forall c, t, s \tag{20}$$

$$\sum_{c=1}^{C} \sum_{l=1}^{C \cup L} \sum_{p=1}^{P} \tilde{d}_{cpts} \leq ca_v Z_v, \quad \forall v, t, s \tag{21}$$

$$U_{mvts} - U_{cvts} + |C| Z_{mcvts} \leq |C| - 1, \quad \forall m, c \in C, v, t, s \tag{22}$$

$$\sum_{c=1}^{C \cup L} Z_{lcvts} = \sum_{c=1}^{C \cup L} Z_{clvts}, \quad \forall v, t, l \in C \cup L, s \tag{23}$$

$$\sum_{l=1}^{L} \sum_{c=1}^{C} Z_{lcvts} \leq 1, \quad \forall v, t, s \tag{24}$$

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$$\sum_{p=1}^{P} V'_{lpts} \leq \sum_{p=1}^{P} ca_{lp} Z_l, \quad \forall l,t,s \tag{25}$$

$$-I_{lcts} + \sum_{u=1}^{C\cup L} (Z_{luvts} + Z_{ucvts}) \leq 1, \quad \forall l,c,v,t,s \tag{26}$$

$$D_{lcvts} \geq t'_{lcv} - M(1 - Z_{lcvts}), \quad \forall\, l,c,v,t,s \tag{27}$$

$$D_{lc'vts} \geq D_{lcvts} + t'_{cc'v} - M(2 - Z_{cc'vts} - I_{lcts}), \quad \forall\, l,c,c',v,t,s \tag{28}$$

$$a_c Z_{lcvts} - D_{lcvts} \leq DT_{cvts} \leq D_{lcvts} - b_c Z_{lcvts}, \quad \forall\, l,c,v,t,s \tag{29}$$

$$Y_{jkpts}, W_{klpts}, U_{lvts}, B_{lcptrs}, T_{klptrs}, Q'_{lptrs}, Q_{kptrs}, DT_{cvts}, D_{lcvts} \geq 0 \tag{30}$$

$$Z_j, Z_l, Z_k, Z_v, I_{lcts}, Z_{lcvts} \in \{0,1\} \tag{31}$$

Equation 1 shows the objective function of the problem. It includes minimizing the costs of the entire supply chain network (facility location selection costs, maintenance costs, drug transportation costs between centers, and fines for exceeding the time window). Relationships (2) to (4) show the amount of drug storage in production centers at the time of drug production according to the time of perishability. Relationships (5) and (6) show the volume of drug transfer from production centers to distribution centers according to the perishability of drugs. Relationships (7) and (8) show the inventory level of each type of drug in the distribution centers, and relationships (9) to (11) lead the inventory level of every kind of drug in the distribution centers at the time of production of each type of drug. Relationships (12) and (13) show the volume of drug transfers from distribution centers to all pharmacies in each period. Equations 14 and 15 guarantee that the demand from pharmacies will be satisfied before the drug's perishability period. Relations (16) to (18) show the maximum capacity utilization of selected suppliers, production centers and distribution centers. Equation 19 shows the total volume of drugs transferred to pharmacies by each distribution center. Equation 20 guarantees that each distribution center can be assigned to only one pharmacy. Equation 21 shows the maximum capacity of the vehicle to distribute medicine to covered pharmacies. Equation 22 is the equation related to sub-tour elimination. The relationship (23) guarantees that the vehicle can visit each pharmacy only once. Relations (24) to (26) ensure that the starting and ending points of vehicle routing in drug distribution to pharmacies are the same distribution centers. Relations (27) and (28) show the time the vehicle arrives at each of the pharmacies. Equation 29 specifies the amount of time for exceeding the time window. Relations (30) and (31) show the types of decision variables.

4. Solution Method

In this research, the pharmaceutical industry's hierarchical supply chain network model consists of three types of NP-Hard problems: location of capacity facilities, optimal flow allocation, and vehicle routing, which have been proven in the literature on their degree of difficulty. Therefore, the degree of difficulty of the model presented in this article is at least equal to that of the aforementioned problems. Therefore, this article uses a combined method of Whale Optimization (WOA) and genetics (GA) called WOGA to solve the problem. Also, the results of this combined algorithm have been compared with each of the results of GA and WOA. In the following, this combined algorithm is discussed.

4.1. WOGA

Humpback whales are one of the largest toothless whales, and their favorite prey are krill and small fish. The most exciting thing about humpback whales is their specific prey. This feeding behavior is called the bubble network feeding method [22]. Humpback whales prefer to hunt schools of krill with small fish close to the surface.

WOA assumes that the best solution candidate is currently the target bait or is close to optimal. After defining the best search agent, other search agents will try to update their position relative to the best search agent. The following equations show this behavior:

$$\vec{D} = |\vec{C}.\vec{X}(t) - \vec{X}(t)| \quad (32)$$

$$\vec{X}(t+1) = \overrightarrow{X^*}(t) - \vec{A}.\vec{D} \quad (33)$$

Where in the above relations t represents the current iteration, $\vec{A}$and $\vec{C}$are coefficient vectors, X^* is the position vector of the best solution obtained so far, and $\vec{X}$is the object position vector. It should be noted that here X^* must be updated in each iteration. If there is a better solution. The vector $\vec{A}$and $\vec{C}$is calculated as follows:

$$\vec{A} = 2\vec{a}.\vec{r} - \vec{a} \quad (34)$$

$$\vec{C} = 2\vec{r} \quad (35)$$

In the above relations, $\vec{a}$decreases linearly from 2 to 0 during repetition and $\vec{r}$ is a random vector [0,1]. According to the type of movement of the humpback whale to hunt the prey (achieving the optimal solution), a spiral equation has been created between the position of the whale and the position of the prey, which is as follows:

$$\vec{X}(t+1) = \overrightarrow{D'}.e^{BL}.Cos(2\pi L) + \overrightarrow{X^*}(t) \quad (36)$$

$\overrightarrow{D'} = |\overrightarrow{X^*}(t) - \vec{X}(t)|$ Is and represents the distance of the ith whale to the prey (the best solution obtained so far), b is a constant defining the shape of the logarithmic spiral, and l is a random number in the interval $[-1,1]$.The humpback whale swims simultaneously around the prey in a reduced circle and along a spiral path.To model this simultaneous behavior, it is assumed that there is a probability of 50 between the encirclement shrinking mechanism and the spiral model used to update the whale's position during optimization. The mathematical model can be expressed as follows:

$$\vec{X}(t+1) = \begin{cases} \overrightarrow{X^*}(t) - \vec{A}.\vec{D} & if\ p < 0.5 \\ \overrightarrow{D'}.e^{BL}.Cos(2\pi L) + \overrightarrow{X^*}(t) & if\ p \geq 0.5 \end{cases} \quad (37)$$

Where p is a random number in the interval [0,1] in addition to the above equations, combination and mutation operators are also used in this article to search the solution space. These operators can change the initial solution to achieve near-optimal results faster. The combination of WOA and GA search operators can lead to exploring more problem spaces. Figures 2 and 3, respectively, show how to perform combination and mutation operators on each solution created in WOA.

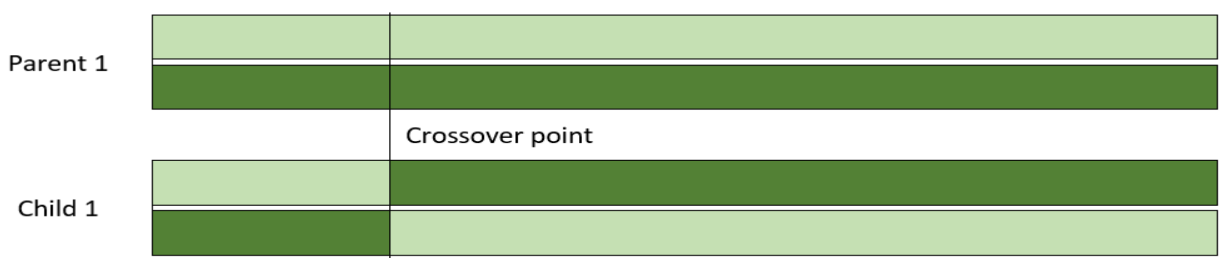

Figure 2.
How to perform the combination operator.

In Figure 2 the combination operator is shown. For each pair of solutions created by WOA, with a probability of 50%, a random point is created between the solutions and the genes of each of the solutions are moved.

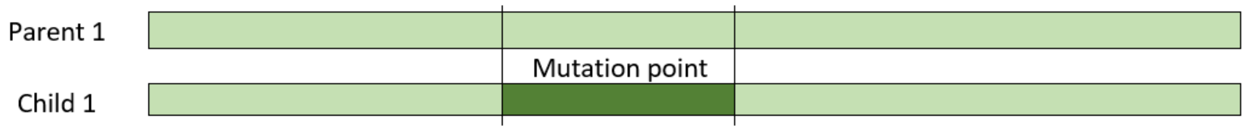

Figure 3.
How the mutation operator works.

In Figure 3, for each of the solutions created in WOA, with a probability of 50%, one of the genes will be removed and a new gene will replace it. Figure 4 also presents the WOGA code.

```
Randomly initialize the whale population
Evaluate the fitness values of whales and find out the best search agent X*
While t < Max it
  Calculate the value of a⃗ according to Eq. (34 & 35)
    For each search agent
        Calculate the new position of whale according to Eq. (36)
          For each pair search agents
              If rand() < 0.5   then use crossover operator according to Fig. (2)
              Else use mutation operator according to Fig. (3)
              End if
          End for
    End for
End while
```

Figure 4.
WOGA code network.

4.2. The Initial Solution

Designing a suitable initial solution is the most important part of implementing any algorithm. In this article, the initial solution is presented as follows due to the existence of different determinations, such as location allocation and routing. Figure 5 considers the initial solution for 2 suppliers, 3 production centers, 3 distribution centers and 5 pharmacies. Also, the number of vehicles is 3.

	Supplier		Production center			Distribution center			Pharmacies				Vehicles		
Node number	1	2	1	2	3	1	2	3	1	2	3	4	1	2	3
Priority	1	2	2	3	1	2	1	3	4	3	2	1	3	1	2

Figure 5.
Initial solution of the mathematical model.

According to Figure 5, the number of elements of the initial solution for the problem is $|P| * |T| * |S| * (|J| + |K| + |L| + |C| + |V|)$. To decrypt, the following steps must be done.

- *Step 1.* The vehicle with the highest priority is assigned to the distribution center with the highest priority (vehicle 1 with priority 3 and distribution center 3 with priority 3).
- *Step 2.* Based on the maximum capacity of the vehicle and the selected distribution center, the sequence of visits to the pharmacies is done according to the highest priority (the sequence of visits for vehicle 1 is "Pharmacy 1 with priority 4, Pharmacy 2 with priority 3, and...").

- *Step 3*. If the medicines are not delivered to all pharmacies due to the vehicle or distribution center's limited capacity, steps 1 and 2 are repeated. If the distribution center is not used, its priority will be reduced to 0.
- *Step 4*. The total volume of drugs transferred by each selected distribution center is calculated.
- *Step 5*. The distribution and production centers are selected with the highest priority, and the volume of the transferred drug is obtained based on the minimum (the amount of demand for the distribution center and the capacity of the production center).
- *Step 6*. If the production center is not used, its priority will be reduced to 0.
- *Step 7*. The total volume of drugs transferred by each selected production center is calculated.
- *Step 8*. The production center and the supplier are selected with the highest priority, and the volume of the transferred drug is obtained based on the minimum (demand value of the production center and the capacity of the supplier).
- *Step 9*. If the supplier is not used, its priority is reduced to 0.
- *Step 10*. The limit of the time window is calculated, and the acceptable amount is determined.
- *Step 11*. The objective function is calculated.

5. Analysis of the Results

5.1. Analysis of Numerical Example in Small Size

After presenting the WOGA, in this section, a small sample problem is designed, including 3 suppliers, 3 production centers, 3 distribution centers, 5 pharmacies, and 2 types of drugs with two vehicles for two time periods in two scenarios. The mentioned numerical example is to check the outputs of the model, which is presented using the exact CPLEX method. Due to the lack of access to real data, random data has been used according to the uniform distribution function, according to Table 1.

Table 1.
Deterministic parameters used in the problem based on uniform distribution.

Parameter	Interval boundaries
E_j, H_k, U_l	$\sim U(10000{,}15000)\$$
F_v	$\sim U(500{,}1500)\$$
θ	$\sim U(4{,}6)\$$
c_l	$\sim U(2{,}3)\$$
t'_{lc}	$\sim U(1{,}8)h$
u_p	$\sim U(1{,}3)h$
$ca_{jp}, ca_{kp}, ca_{lp}$	$\sim U(500{,}1000)n$
ca_v	$\sim U(1000{,}1200)n$
p_s	0.5
$\tilde{t}_{jks}, \tilde{t}_{kls}, \tilde{t}_{lcs}$	$for\ s=1 \sim U(5{,}10)\$ ----for\ s=2 \sim U(7{,}12)\$$
$\tilde{h}_{ks}, \tilde{h}'_{ls}$	$for\ s=1 \sim U(2{,}4)\$ ----for\ s=2 \sim U(7{,}12)\$$
$\tilde{d}_{cpts}$	$for\ s=1 \sim U(150{,}200)n ----for\ s=2 \sim U(170{,}220)n$

After solving the mathematical model with CPLEX, the value of the objective function of the problem is equal to \$124533.46 in a time of 129.74 seconds. Figure 6 shows the best way for the vehicle to travel and for goods to move between the different levels of supply chain in each of the scenarios shown in this numerical example. Figure 6 shows that the number of centers selected for drug supply to pharmacies is the same in both scenarios. The vehicle routing is different from each other according to the change of the demand amount in the two scenarios.

Table 2 shows the type of vehicle selected for drug distribution as well as the arrival time of each vehicle to pharmacies.

Table 2 shows that the vehicles were responsible for the distribution of drugs to pharmacies within the predefined time window. Next, with the change in the probability of different scenarios, the costs of the entire supply chain network are shown in Table 3.

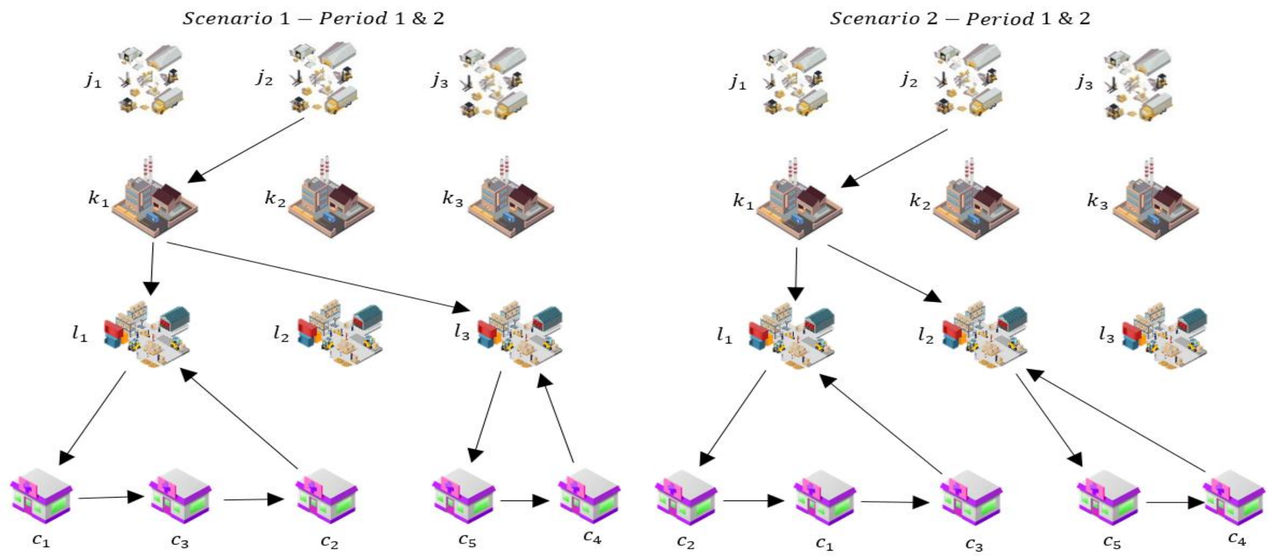

Figure 6.
Routing-locating-assignment in a hierarchical supply chain.

Table 2.
Arrival time of the selected vehicle to each pharmacy.

	Pharmacy	**1**	**2**	**3**	**4**	**5**
	Time window	[7---10]	[8---13]	[10---13]	[10---12]	[4---6]
Scenario 1 – Period 1 & 2	Vehicle number → Time arrival	$v_1 \rightarrow 7.82$	$v_1 \rightarrow 12.32$	$v_1 \rightarrow 10.88$	$v_2 \rightarrow 11.89$	$v_2 \rightarrow 5.54$
Scenario 2 – Period 1 & 2		$v_1 \rightarrow 9.58$	$v_1 \rightarrow 8.11$	$v_1 \rightarrow 12.64$	$v_2 \rightarrow 11.70$	$v_2 \rightarrow 5.33$

Table 3.
Costs of the entire supply chain network in the probability of different scenarios.

Scenario		**Total cost**	**Changes %**
p_1	p_2		
0.1	0.9	136584.94	9.677
0.2	0.8	132744.60	6.594
0.3	0.7	128643.26	3.300
0.4	0.6	126997.67	1.979
0.5	0.5	124533.46	0.000
0.6	0.4	121445.97	-2.479
0.7	0.3	118692.07	-4.691
0.8	0.2	115677.67	-7.110
0.9	0.1	112346.99	-9.786

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The results of Table 3 show that with the increase in the probability of the second scenario, the demand of pharmacies for different drugs has increased, leading to an increase in the costs of transportation, production, distribution, etc. The time of corruption considered to solve the above problem is 2, and the total cost of the supply chain network is equal to $124533.46. To check the total costs, the period of corruption 1-6 is considered, and the resulting changes are shown in Table 4.

Table 4.
The amount of changes of the first and second objective functions with the change of the period of time corruption.

u_p	Total cost	Changes %
1	155611.5	24.96
2	124533.5	0.00
3	113289.1	-9.03
4	112772.3	-9.44
5	112772.3	9.44
6	112772.3	-9.44

According to the sensitivity analysis performed on the period of corruption, the total cost of the network reaches its highest level if the time period of corruption is 1. Because in this case, the production and distribution centers cannot have inventory in their warehouses and must meet the demand of pharmacies in every period of time. It can also be seen that the cost of the entire network has decreased with the increase in the time period of corruption. This is due to proper planning in inventory maintenance. Because the total time period of 2 is considered, when the perishability period is greater than the time period, a behavior similar to the perishability of a1-time period works.

Figure 7 shows the sensitivity analysis performed in different scenarios and periods of corruption.

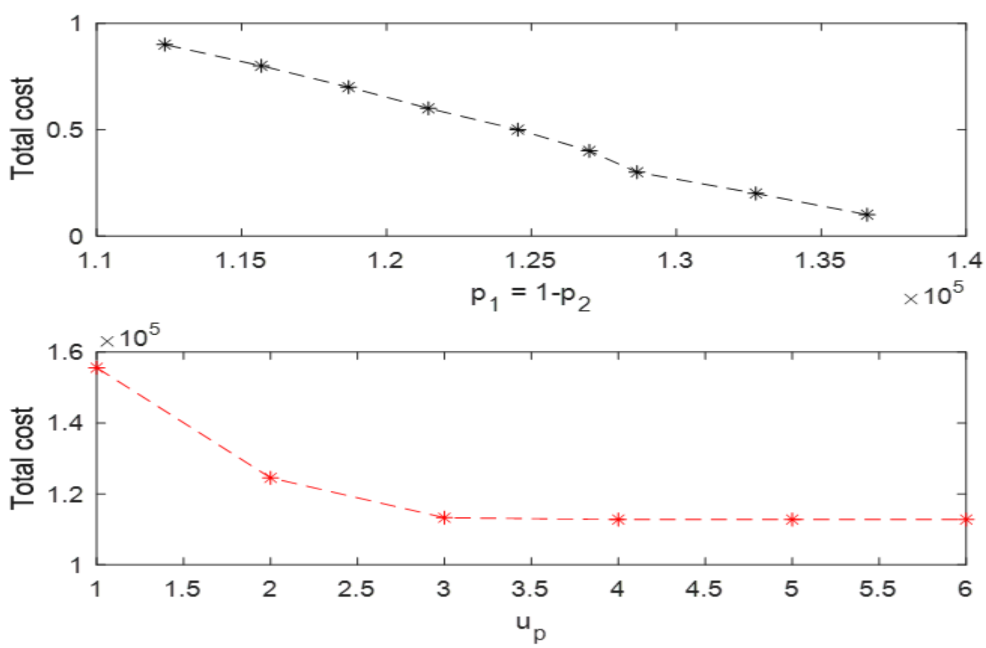

Figure 7.
Sensitivity analysis of the issue in the scenario under different periods of corruption.

For more sensitivity analysis on the model, the capacity parameter of the production center is also taken into account, the changes of that cause changes in the total costs. Therefore, the value of the capacity of the production center is 10, 20, 30, 40, and 50% less and more than the basic capacity, and the values of the obtained objective functions are shown in Table 5.

Table 5.
The amount of changes in the objective functions with the change in the capacity of the production center.

Production center capacity changes %	Total cost	Changes %
-50 %	167498.62	34.50
-40 %	167498.62	34.50
-30 %	167498.62	34.50
-20 %	124533.46	0.00
-10 %	124533.46	0.00
0	124533.46	0.00
+10 %	124533.46	0.00
+20 %	109539.98	-12.04
+30 %	109539.98	-12.04
+40 %	109539.98	-12.04
+50 %	109539.98	-12.04

According to the results of Table 5, it can be seen that with the increase in the capacity of the production center, a smaller number of production centers is needed, and this issue has led to a reduction in the costs of the entire supply chain network. Due to the NP-Hardness of the mathematical model due to the integration of location-routing-allocation problems, the analysis of the numerical example provided with WOGA has been discussed in the following: Due to the proposed algorithm's combination, this method's results have been compared with GA, WOA, and CPLEX. Therefore, Figure 8 shows the convergence of meta-heuristic algorithms in solving the mathematical model in 100 consecutive iterations.

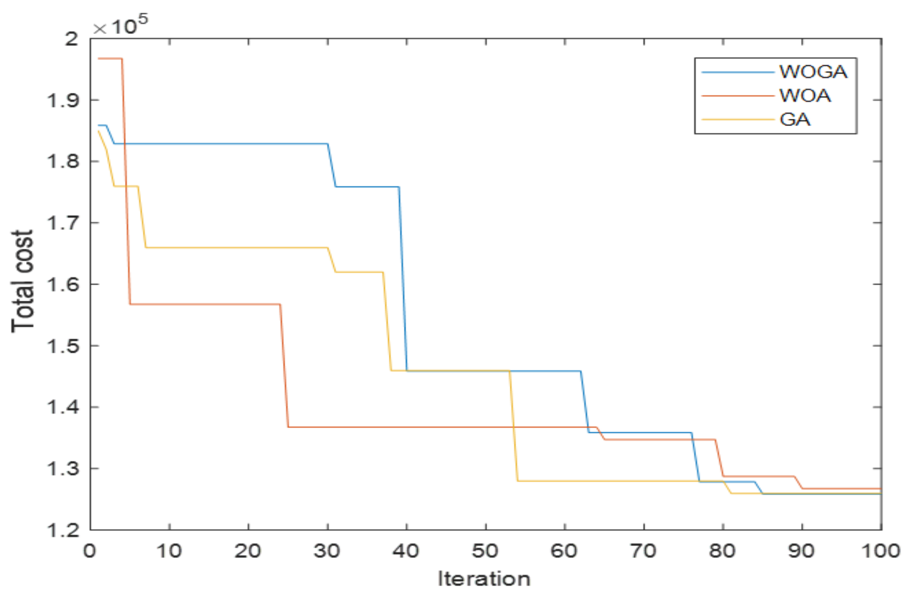

Figure 8.
Convergence of optimization algorithms in achieving a near-optimal solution.

Figure 8 displays the optimal value of the objective function after 100 iterations using various methods. Based on this, the total costs obtained by WOGA are equal to 125876.44, by WOA they are equal to 126744.37, and by GA they are equal to 125974.61. Therefore, the highest percentage of relative difference between the results of meta-heuristic algorithms and CPLEX is equal to 1.77%.

5.2. Validation of the Model

The capacity of the stochastic programming approach to capture showcase vulnerabilities is assessed using EVPI (the expected value of perfect information) and VSS (the value of the stochastic solution). The EVPI degree is decided as the contrast between irregular arrangements and wait-and-see (WS) arrangements, and it appears how profitable it is to know the long run with total certainty. For this reason, the sum of requests within the various leveled supply chain arrangements within the pharmaceutical industry has been examined, and the normal esteem of EVPI, which is the result of the distinction between the coming about of arbitrary arrangements and the anticipated arrangements (EVPI=WS-SP), is shown in Table 6. Table 6 presents the value of the EVPI file when the request is considered a questionable parameter. To calculate the esteem of EVPI, to begin with, the stochastic issue is fathomed for each situation independently. According to the ideal arrangement and the probabilities of each situation, weighted midpoints are calculated for all arrangements, which speak to the WS arrangement. EVPI is, at that point, calculated as the contrast between the WS and SP irregular arrangements. Moreover, VSS is calculated and characterized as the supreme contrast between the EEV and SP arrangements to determine the preferences for utilizing the stochastic programming approach over the deterministic approach. In this case, the higher value of VSS shows that the stochastic programming approach can deal with uncertainty in the network. To calculate EEV, instead of non-deterministic parameters, the average of the expected data is used in the model to represent the deterministic state of the network.

Table 6.
Value of EVPI (The expected value of perfect information) and VSS (The Value of the Stochastic Solution) when demand is uncertain as a parameter.

Algorithm	SP	WS	EVPI	EEV	VSS
CPLEX	124533.46	126825.67	2292.21	123718.67	814.79
WOGA	125876.44	127675.17	1798.73	124964.83	911.61
WOA	126744.37	127983.32	1238.95	125934.73	809.64
GA	125974.61	126985.73	1011.12	124927.77	1046.84

The results of Table 6 show that uncertainty in demand compared to supply has a more significant impact on supply chain network planning. Therefore, managers should bear more costs to achieve high network accuracy. The VSS for the total charges in different solution methods, on the other hand, is positive. This means that the stochastic approach is more reliable when dealing with the uncertain environment for the pharmaceutical industry's hierarchal supply chain.

5.3. Analysis of Numerical Examples of Larger Size

It is because meta-heuristic algorithms, like WOGA, are very good at solving small numerical examples that we will now talk about how to analyse larger numerical examples. For this purpose, 15 numerical examples in a larger size have been designed according to Table 7. The data used in numerical examples is random, according to Table 1.

Each numerical example is solved three times by WOGA, GA, and WOA, and the best solution of the objective function (lowest total cost of the network) is shown in Table 8. Meta-heuristic algorithms also show the best values of the objective functions of problem-solving time in Figure 9.

Table 7.
Size of numerical examples in larger size.

#	$(\lvert J\rvert * \lvert K\rvert * \lvert L\rvert * \lvert C\rvert * \lvert P\rvert * \lvert V\rvert * \lvert T\rvert * \lvert S\rvert)$	#	$(\lvert J\rvert * \lvert K\rvert * \lvert L\rvert * \lvert C\rvert * \lvert P\rvert * \lvert V\rvert * \lvert T\rvert * \lvert S\rvert)$
1	$(4*4*4*6*2*2*3*2)$	9	$(10*10*12*28*2*2*3*2)$
2	$(5*5*5*8*2*2*3*2)$	10	$(10*15*12*32*2*2*3*2)$
3	$(5*5*6*10*2*2*3*2)$	11	$(10*15*15*36*2*2*3*2)$
4	$(6*6*6*12*2*2*3*2)$	12	$(12*15*18*38*2*2*3*2)$
5	$(6*6*8*15*2*2*3*2)$	13	$(12*18*21*42*2*2*3*2)$
6	$(8*8*8*18*2*2*3*2)$	14	$(15*18*21*45*2*2*3*2)$
7	$(8*8*10*21*2*2*3*2)$	15	$(15*21*25*50*2*2*3*2)$
8	$(8*10*12*25*2*2*3*2)$		

Table 8.
The best value of the objective function in large size numerical examples.

Sample problem	CPLEX	WOGA	WOA	GA
1	179257.33	180873.74	182280.85	180534.25
2	228574.33	239900.90	239138.47	240419.04
3	268749.34	278119.60	277297.4	275381.47
4	387948.34	408643.34	410498.89	410239.38
5	501453.92	515459.99	515545.74	520242.83
6		670152.91	668758.83	667401.77
7		750236.04	752280.13	757318.35
8		815825.55	820559.93	813715.83
9		902820.99	898514.02	907183.92
10		1041395.60	1043873.8	1045113.3
11		1161240.54	1166689.6	1167009.9
12		1239885.13	1244906.1	1242623.5
13		1390526.66	1401658.0	1380751.3
14		1406472.86	1419011.3	1403350.3
15		1517575.55	1510511.6	1514354.6

According to the results of Table 8, it can be seen that with the increase in the size of the problem due to the increase in the number of pharmacies and the demand for different drugs, the costs of the entire hierarchical supply chain network, including location-routing and allocation, have increased. It can also be seen that CPLEX does not have the ability to solve sample problems larger than number (5). This is because the mathematical model is NP-hard.

According to the results obtained from solving numerical examples in larger sizes, it was observed that, on average, the total costs obtained from the WOGA method are lower than other meta-heuristic methods. If this method has a higher solution time than other proposed methods in terms of using different operators. To figure out how to solve this problem, we looked at the big differences in the averages of the objective function and the amount of the time it look to compute for each method in Table 9's numerical examples. The test used for this comparison is two-sided T-test.

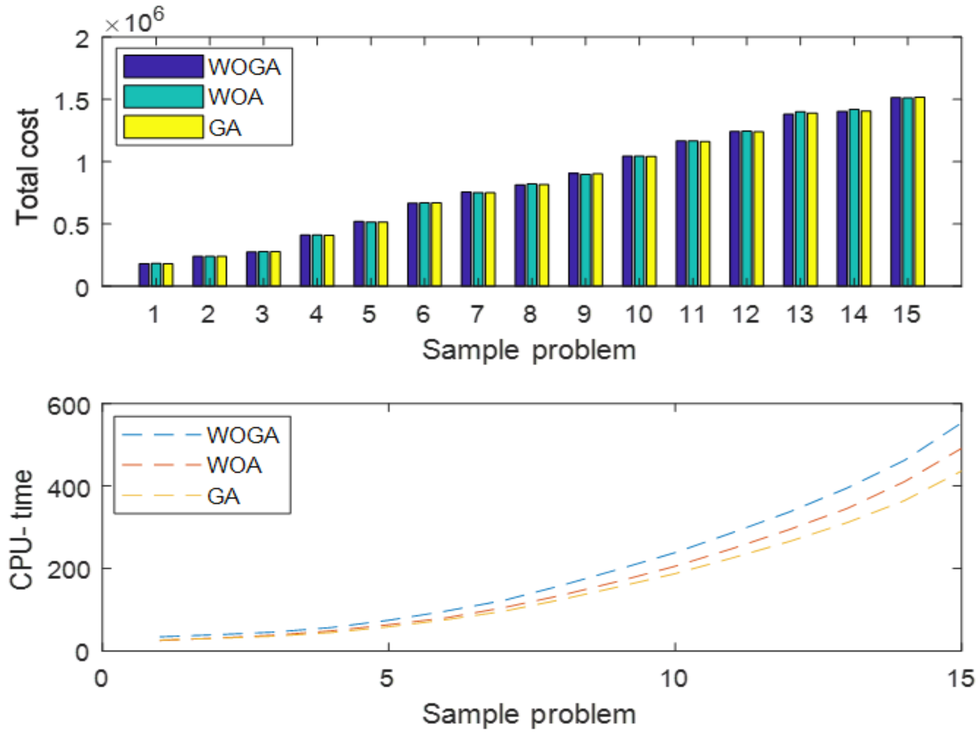

Figure 9.
Results obtained from solving sample problems in larger sizes.

Table 9.
Examining the significant difference of the averages of indicators with T-test.

Index	Algorithm	Difference	95% CI for difference	T-value	P-value
Total cost	WOGA-WOA	2160	(-339685, 335366)	0.01	0.990
	WOGA-GA	434	(-336889, 336021)	0.00	0.998
	WOA-GA	1726	(-335438, 338889)	0.01	0.992
CPU-time	WOGA-WOA	27.2	(-91.4, 145.7)	0.47	0.642
	WOGA-GA	44.0	(-68.9, 157.0)	0.80	0.430
	WOA-GA	16.9	(-88.5, 122.2)	0.33	0.745

According to the results of Table 9, it can be seen that the P-Value among the averages of the total cost index and computing time between all algorithms is greater than 0.05. This issue shows the absence of significant differences between the averages of the calculation indices. Figure 10 also shows the comparison chart of the one-way ANOVA test among the comparison indicators.

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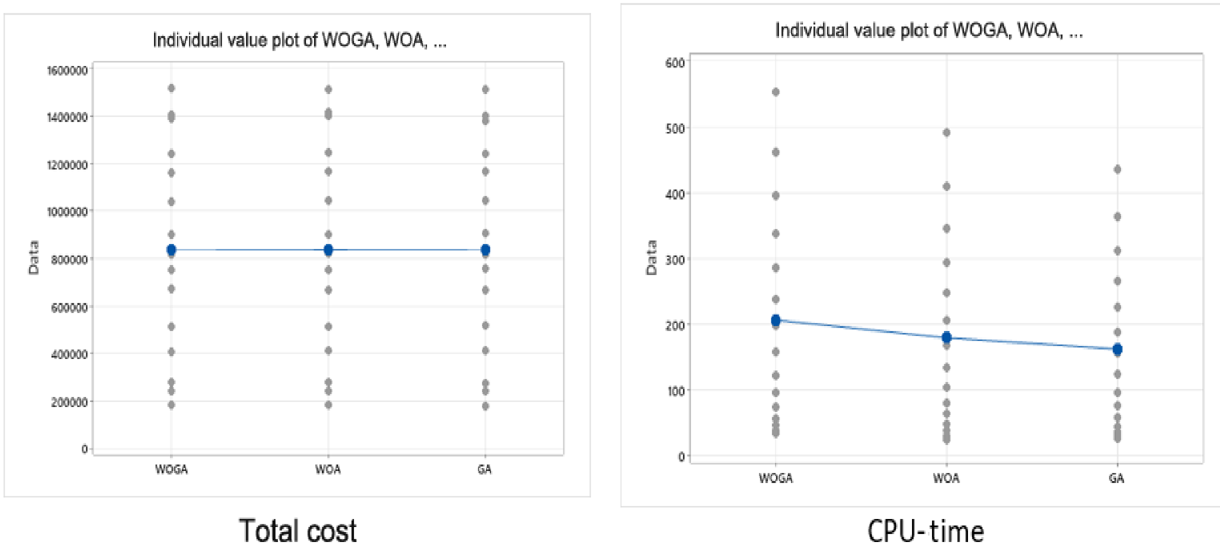

Figure 10.
One-way ANOVA comparison chart.

Since there wasn't a big difference in the average calculation times, we can say that WOGA is a better way to solve the hierarchal supply chain problem in the pharmaceutical industry and get better results than other methods that have been tried.

6. Conclusion

The importance of drug supply and the efficiency and effectiveness of the hierarchical drug supply chain as a strategic commodity are not hidden from anyone. Therefore, the way to supply raw medicine materials, production, storage, and distribution of medicine in a supply chain network is very important. With the aim of covering all aspects of drug supply and distribution, this article presents a hierarchical network of the supply chain in which facility location decisions, optimal flow allocation, and vehicle routing were made simultaneously. The objective function considered for the mathematical model included minimizing total costs. Due to the uncertainty of demand parameters, drug transportation, and storage costs, the two-stage probabilistic programming method was used to model the problem, and the results showed that the use of this method has higher reliability to face uncertainty. By analyzing the mathematical model and examining the problems, it was observed that the total cost of the network reaches its highest level if the time period of corruption is 1. Because in this case, the production and distribution centers cannot have inventory in their warehouses and must meet the demand of pharmacies in every period of time. It was also observed that with the increase in the time period of corruption, the total cost of the network has decreased. This is due to proper planning in inventory maintenance.

Exact solution methods could not provide the desired results for the presented model, and therefore, other methods were used to solve the problem. In this article, WOGA, which is a combination method of two different algorithms, is presented. The results of solving the mathematical model with this and other methods showed that strategic and tactical decisions have the lowest costs when they are taken with WOGA. This method had a higher search rate than other solution methods. We saw that the P-value for the difference in the total cost and computing time index between algorithms (WOGA-WOA-GA) is greater than 0.05 when we looked at the results of the T-test on large sets of numbers. This issue shows the absence of significant differences between the averages of the calculation indices.

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Transparency:
The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

Competing Interests:
The authors declare that they have no competing interests.

Authors' Contributions:
Both authors contributed equally to the conception and design of the study. Both authors have read and agreed to the published version of the manuscript.

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