IRAQI Academic Scientific Journals
العراقية المجلات الاكاديمية العلمية
Al-Kut University College Journal
ISSN (E) : 2616 - 7808 II ISSN (P) : 2414 - 7419
https://js.alkutcollege.edu.iq/
k.u.c.j.sci@alkutcollege.edu.iq
Special Issue - The 6th Scientific Conference of Al-Kut University College - 2-3 May 2023

# An Observational Study of the Current Situation with Wasit City Pharmacies that Dispense Compounded (Fixed Dose Combination) Medications for Hypertension and Diabetes

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## Abstract

**Background:** One of the most recent advances in drug design and delivery is the introduction of combined drugs, also known as fixed dose combinations (FDC), which have numerous benefits for patients and pharmacists.

**Objectives:** The purpose of this study was to evaluate the FDCs available in Wasit-Government pharmacies for the treatment of chronic diseases such as hypertension and diabetes mellitus.

**Methods:** The drug information was obtained from the drug sheet contained in the drug pack, which included the generic and brand names, constituents, route of administration, manufacturer, and country sources.

**Results:** The proportion of FDCs was 33.7 (127 out of 377 drugs). Patients with chronic diseases received 24 out of 127 prescriptions (18.9%). The sources of 23 drugs were 19 pharmaceuticals from 16 countries, and the source of one FDC was unknown. Only 11 FDCs were recommended for the treatment of hypertension (n=5) and diabetes (n=6).

**Conclusion:** The main barriers to the value of long-term use of FDCs in hypertension and diabetes management were a lack of available and inadequate resources for FDCs.

**Keywords:** Fixed dose combination, Long-term users, Hypertension, Diabetes mellitus, Resources

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**Paper Info.**
**Published:** Aug. 2023

# دراسة رقابية حول الوضع الحالي في صيدليات محافظة واسط التي توصف الأدوية المؤتلفة (مجموع الجرع الثابتة) لمرضى ارتفاع ضغط الدم والسكري

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## المستخلص

**الخلفية:** تعد توليفة الدواء والمعرفة بمجموع الجرع الثابتة من التقدم الحديث في تصميم وتسويق الدواء لما يتصف بفوائد لكل من الصيادلة والمرضى.

**هدف الدراسة:** هدفت الدراسة الى تقييم أدوية "مجموع الجرع الثابتة" والمتوفرة قي صيدليات محافظة واسط والتي توصف لمرضى ارتفاع ضغط الدم والسكري.

**طرائق العمل**: تم استحصال المعلومات المدونة في اللائحة الصيدلانية الموجودة في العبوة الدوائية والتي تضمنت الأسم العلمي والتجاري للدواء، مكونات الدواء، طرق اعطاء الدواء، الشركة المصنعة ومصادر

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معلومات البحث
تاريخ النشر: آب 2023

انتاج الدواء .

**النتائج:** بلغت نسبة أدوية "مجموع الجرع الثابتة" المتوفرة 33.7% ( 127 من أصل 377 دواء) وكانت حصة الأدوية التي توصف لمرضى ارتفاع ضغط الدم والسكري فقط 24 من أصل 127 (18.9%). لقد كان منشأ 23 دواءا يعود الى 19 شركة صيدلانية متوزعة على 16 دولة في حين كان أحد الأدوية مجهول الشركة والدولة المنتجة . كانت حصة أدوية "مجموع الجرع الثابتة" لمرضى السكري 6 ولمرضى ارتفاع ضغط الدم 5 فقط.

**الأستنتاج:** ان العوز في توفر أدوية "مجموع الجرع الثابتة" وكون مصادرها غير كافية من الحواجز الرئيسية التي تقييم استعمال مقل هذه الأدوية على المدي البعيد في معالجة السكري وارتفاع ضغط الدم.

**الكلمات المفتاحية :** مجموع الجرع الثابتة، استعمال طويل الأمد، ارتفاع ضغط الدم، السكري، مصادر

## Introduction

Fixed dose combinations (FDCs) are defined as a combination of two or more active ingredients within a single form of pharmaceutical administration [1, 2]. They have been shown to appreciably reduce the risk of medication non-adherence, which is particularly important in patients with chronic diseases [3]. However, their rationality for use should be based on sound medical principles, as there have been concerns with their irrationality and utility in several countries [4, 5]. The advantages and disadvantages of the FDCs depend on the disease targeted by the pharmaceutical formulation and aim to produce synergism and less toxic effects. Inadequate FDC manufacturing can result in a decreased efficacy or increased toxicity in routine clinical care, as well as peak efficacy at different times and shelf life concerns [6]. FDCs are used in a variety of ways in the treatment of hypertension. An FDC of valsartan and amlodipine (80/5mg) was reported to reduce blood pressure better than valsartan monotherapy of 160 mg and was well tolerated by patients [7]. Another study compared the efficacy of two FDCs in the treatment of uncontrolled hypertension, finding that irbisartan/hydrochlorthiazide (150/12.5mg) was more effective than valsartan/hydrochlorthiazide (80/12.5mg) and comparable to losartan/hydrochlorthiazide (50/12.5mg) [8]. Some studies mentioned the use of fixed-dose triple combination therapy, which included the renin-angiotensin-aldosterone pathway (either a direct renin inhibitor or an angiotensin II receptor blocker) in combination with a calcium channel blocker and diuretic, and demonstrated better blood pressure control and patient tolerance [9]. Another approach is to use an FDC of amlodipine and atorvastatin (a lipid-lowering agent) to prevent the late unfavorable consequences of uncontrolled hypertension, such as stroke, myocardial infarction, and so on [10]. Some authors believed that improving FDCs implementation in country-specific health systems was necessary in terms of improving FDCs availability, accessibility, affordability, and adherence. FDCs could be included in the WHO HEARTS technical package; treatment and monitoring algorithms could be simplified; medicine dispensing which could be decentralized; and task-sharing for treatment management could be implemented [11]. Various classes of non-insulin hypoglycemic agents or a combination of one of these classes with other drugs such as lipid-lowering agents can improve

diabetes control and treat co-morbidities. Combination therapy with SGLT2 inhibitors had a statistically significant impact on HbA1c% reduction in patients with T2DM when compared with monotherapy [12]. Because of the unique mechanism of action and low risk of hypoglycemia with SGLT2 inhibitors, the combination of SGLT2 inhibitors and other oral antidiabetes complements, for example, dapagliflozin and empagliflozin, is beneficial [13, 14]. Safety studies have also revealed that SGLT2 inhibitor combination therapies were well tolerated and did not result in any serious adverse events (e.g., renal impairment, fractures, malignant neoplasms, and volume-related events) [15, 16]. A FDC of SGLT2 inhibitors and metformin resulted in a complementary action, and neither of these compounds targets pancreatic cells, increases body weight, or poses significant safety risks [17]. A systematic review of 14 studies found that combining an SGLT2 inhibitor (dapagliflozin) with metformin resulted in lower HbA1c levels, weight loss, and a 3-5 mmHg decrease in systolic blood pressure in patients with T2D [18]. Recently, an FDC containing insulin glargine (100U/mL) and lixinatide (a glucagon-like peptide 1 receptor agonist) significantly improved HbA1c% and insulin secretion and beta-cell function when compared with lixinatide monotherapy [19].

Simvastatin and sitagliptin FDC have been shown to improve adherence by reducing pill burden, treatment regimen complexity, and, potentially, cost. This combination will mitigate the negative effects of dyslipidemia co-morbidity in diabetes patients [20]. The rationale for this study is that most studies encourage physicians to use FDCs instead of single formulations or add-on therapies approach in the management of chronic diseases such as diabetes mellitus and hypertension, and these studies emphasized the importance of including these therapies on the WHO-essential drug list. The efficacy, well tolerance, high adherence rate, and lack of pill burden are the reasons for such a claim.

This studying aimed to clarifying the status of FDCs in Wasit-Government at pharmacies and to demonstrate that such therapies meet the needs of patients, taking into account the uses of FDCs in the management of diabetes mellitus and hypertension, as these long-standing diseases with comorbidities required long-term therapy, which caused patients not to adhere to the medicine.

## Materials and Methods

The scientific committee in the Department of Pharmacy at Kut University College approved this study as a part of a research proposal for 5th year undergraduate students. From November 1, 2022 to December 31, 2022, a total number of 377 drug leaflets was collected from pharmacies in Iraq's Wasit Governorate (Figure 1: Flow chart). From each sheet, the following information was extracted: the generic and brand names of the drugs; the constituents of the fixed drug combination (in tablet or capsule form); the name of the manufacturer; and the country of the drug company. The outcomes were expressed as numbers, percentages, and ratios.

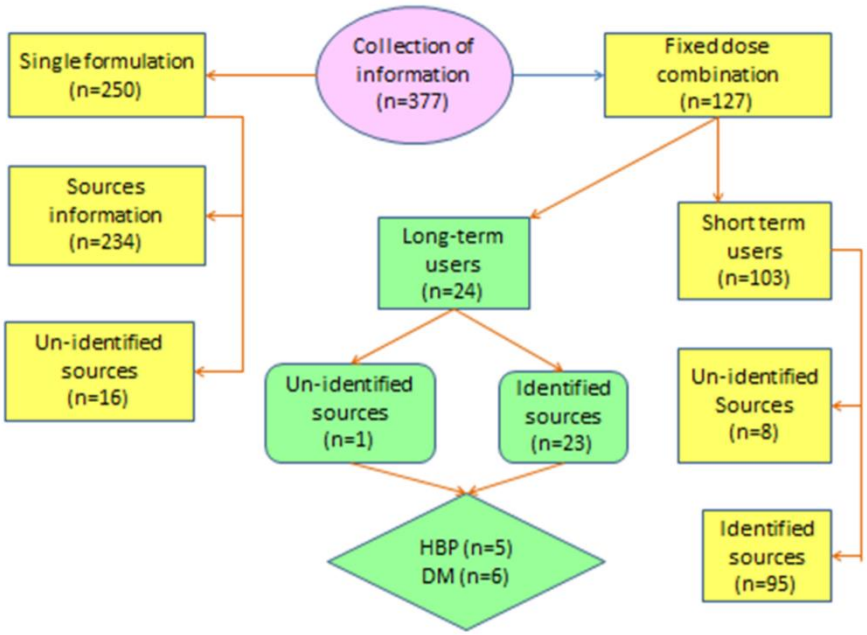


**Figure 1: HBP: Hypertension, DM: Diabetes**

## Results

A total of 377 drug sheets were gathered. Figure 2 shows that a single formulation drugs accounted for 66.3% (250 out of 377) of all drugs, while FDCs accounted for 33.7%. The drug company, its country, or both did not identify the sources of 25 medicines; 16 were single formulations and 9 were FDCs (Figures 3 and 4). One in every nine FDCs is prescribed for chronic diseases. 4.2% of FDCs from unidentified sources are prescribed for chronic diseases (1 out of 24).

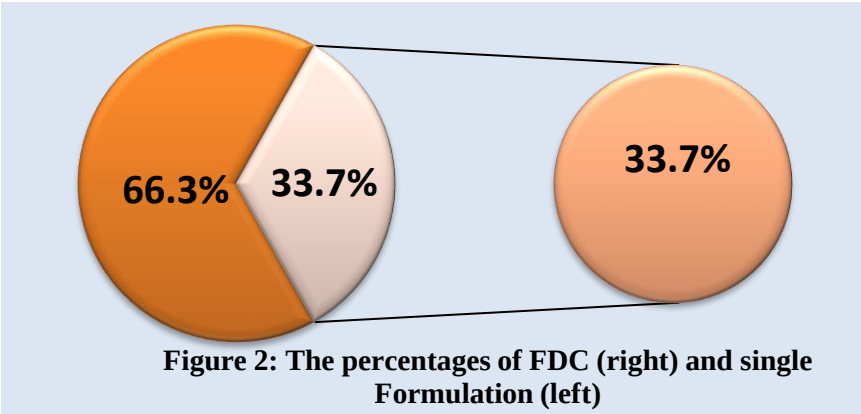


**Figure 2: The percentages of FDC (right) and single Formulation (left)**

The distribution of 127 FDCs according to their sources is shown in Table 1. Pharmaceutical companies located in Iraq are the sources of 15 out of 127 (11.8), and only three FDCs were licensed by foreign pharmaceutical companies to Iraqi pharmaceuticals in the Kurdistan Region. 87

pharmaceutical companies imported or manufactured 118 FDCs (1.356 drugs per pharmaceutical company), while 9 FDCs lacked pharmaceutical information. 19 pharmaceutical companies cover 23 long-term FDCs (1.21 drugs per pharmaceutical). 108 companies imported or manufactured 234 single formulations (2.167 drugs per pharmaceutical company), while 16 single formulations lacked pharmaceutical information (Figure 5). The constituents of each FDC used in the management of diabetes mellitus (6), hypertension (6), birth planning (5), irritable bowel syndrome (3), rheumatoid arthritis (2), depression (1), and glaucoma (1) are shown in Table 2.

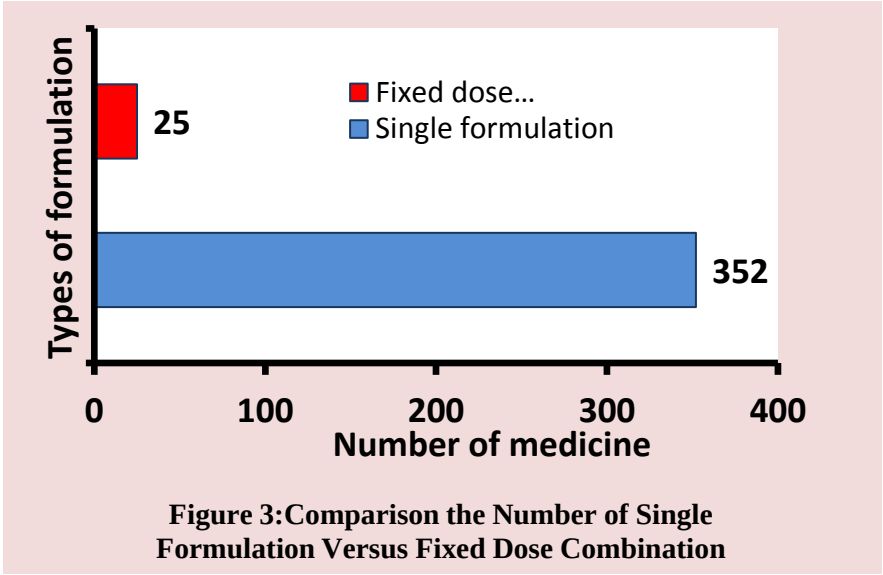


**Figure 3:Comparison the Number of Single Formulation Versus Fixed Dose Combination**

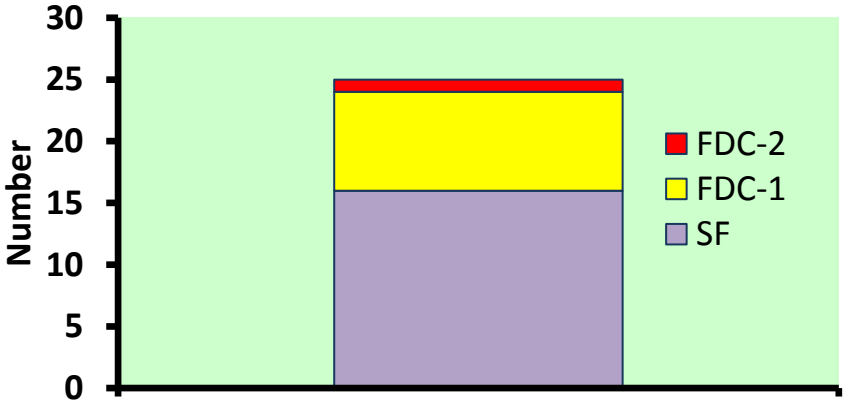


**Figure 4: Distribution of Drugs according to their Prescription Formula.**

(SF: single formulation, FDC-1: fixed dose combination forshort term use, and FDC-2: for long term use)

**Table 1: Sources of fixed dose combination imported to Iraq**

| Country | No. | |
|---|---|---|
| | General | Chronic |
| Argentina | 2 | 1 |
| Belgium | 1 | 0 |
| Denmark | 1 | 1 |
| Egypt | 18 | 2 |
| England | 5 | 1 |
| France | 2 | 1 |
| Germany | 10 | 5 |
| India | 17 | 1 |
| Iran | 1 | 1 |
| Iraq (including Kurdistan ) | 15 | 3 (Licensed to pharmaceuticals in Kurdistan Region) |
| Italy | 2 | 0 |
| Jordan | 9 | 2 |
| Pakistan | 2 | 1 |
| Lebanon | 1 | 0 |
| Macedonia | 1 | 0 |
| Saudi Arabia | 4 | 1 |
| Slovenia | 1 | 0 |
| Spain | 2 | 0 |
| Sultanate Oman | 1 | 0 |
| Switzerland | 2 | 1 |
| Syria | 9 | 0 |
| Netherland | 1 | 1 |
| Tunisia | 1 | 0 |
| Turkey | 3 | 1 |
| UAE | 4 | 0 |
| Ukrania | 1 | 0 |
| USA | 2 | 0 |
| Un-identified | 9 | 1 |
| **Total** | 127 | 24 |

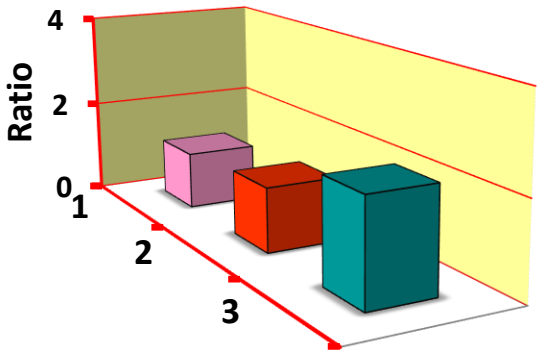


**Figure 5: The Ratio of Drug Number Provided by Pharmaceuticals**
1: FDC-long term, 2: FDC-short term and 3: Single formulation

**Table 2: The constituents of FDCs that prescribed to patients with chronic illnesses (Long-term users)**

| Disease | No. | Fixed drug combinations |
|---|---|---|
| Hypertension | 5 | Losartan potassium + Hydrochlorthiazide<br>Valsartan hydrochlorthiazide<br>Valsartan +amlodipine<br>Bispropol fumerate + hydrochlothiazide<br>Valsartan +amlodipine |
| Diabetes mellitus | 6 | Vildagliptin + Metformin<br>Dapagliflozin + Metformin<br>Sitagliptin + Metformin<br>Vildagliptin + metformin<br>Glibenclamide + metformin<br>Empagliflozin + metformin |
| Birth planning | 5 | Estradiol valearate + Norgestrel<br>Ethinyl + Drospirenone<br>Ethyestradiol + Gestodene<br>Levonorgestrol + Ethinylestradiol<br>Desogestrel + Ethinylestradiol |
| Irritable bowel syndrome | 3 | Mebeverine HCl + Sulipride<br>Mebeverine HCl + Sulipride<br>Mebeverine HCl + Sulipride + Simethicone |
| Depression | 1 | Flupentixol + Melitracen HCl |
| Glaucoma | 1 | Dorzolamide HCl + Timolol maleate |
| Rheumatoid arthritis | 2 | Diclofenac sodium + Predinosolone + cyanocobalamine<br>Diclofenac sodium+ Chlorzoxazone +Paracetamol |

## Discussion

The findings revealed three flaws in the FDC drugs dispensed in pharmacies. First, the resources for these medicines revealed that one FDC is available in the pharmacy without evidence of the pharmaceutical company's name or the country of origin. This was not previously reported with FDCs, but it could happen with illicit drugs distributed in corrupted communities [21]. There is no doubt that such medicine will be harmful to patients because the constituents of medicines that comprise FDC pills are unknown [22]. Second, out of 127 FDCs, 24 were available in pharmacies, indicating that 103 were related to short-term remedies, such as for upper respiratory tract infections, multivitamins, or analgesics. Most countries encourage the use of CFSs for diabetes, hypertension, and cancer for reasons related to cost, adherence, and efficacy [23-26]. Furthermore, the sources of FDCs should be of high quality and subjected to a promising assay, which some of the FDCs reported in the study lack [27, 28]. Third, the types of FDCs imported to these pharmacies are limited and differ from those reported globally, which suggest that health providers lack knowledge about the benefits of using DFCs [29, 30]. This study discovered that there is a shortage of FDCs being imported and that some of these products are inadequate; additionally, one product is of unknown origin. One significant limitation is the small number of drugs available, and the drugs on the Ministry of Health's list were not included. Due to security concerns, these restrictions cannot be avoided.

## Conclusions

The main impediments to the value of long-term use of FDCs in hypertension and diabetes management were a scarcity of FDCs and insufficient FDC resources.

## References

[1] C.S. Gautam, L. Saha. Fixed dose drug combinations (FDCs): rational or irrational: a view point. *Br J Clin Pharmacol*, vol.65, pp. 795-796, 2008.

[2] EMA (European Medicine Agency). Guideline on clinical development of fixed combination medicinal products. 2017 [cited 2019 Oct 10]. Available from https://www.ema.europa.eu/en/documents/scientific-guideline/guidelineclinical-development-fixed-combination-medicinal-productsrevision-2_en.pdf

[3] S. Bangalore, G. Kamalakkannan , S. Parkar S, F.H. Messerli. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*, vol.120, pp. 713-719, 2007.

[4] D. Sawicki-Wrzask, M. Thomsen, O.J. Bjerrum. An analysis of the fixed-dose combinations authorized by the European Union, 2009-2014: A focus on benefit-risk and clinical development conditions. *Ther Innov Regul Sci*, vol. 49, pp. 553-559, 2015.

[5] B. Błaszczyk, B. Miziak, P. Czuczwar, E. Wierzchowska-Cioch, R. Pluta, S.J. Czuczwar. A viewpoint on rational and irrational fixed-drug combinations. *Expert Rev Clin Pharmacol*, vol.11, pp. 761-771, 2018

[6] Y.K. Gupta, S.S. Ramachandran SS. Fixed dose drug combinations: Issues and challenges in India. *Indian J Pharmacol*, vol. 48, pp. 347-349.

[7] K.L. Wang, W.C. Yu, T.M. Lu, L.C. Chen, H.B. Leu, C.E. Chiang. Amlodipine/valsartan fixed-dose combination treatment in the management of hypertension: A double-blind, randomized trial. *J Chin Med Assoc.*, vol. 83, pp. 900-905, 2020.

[8] Bramlage P. Fixed combination of irbesartan and hydrochlorothiazide in the management of hypertension. *Vasc Health Risk Manag*, vol. 5, pp. 213-224, 2009

[9] B.J. Epstein, N.K. Shah, N.L. Borja-Hart. Management of hypertension with fixed-dose triple-combination treatments. *Ther Adv Cardiovasc Dis*, 2013;7(5):246-259.

[10] C.P. Lin, Y.C. Tung, F.C. Hsiao, C.H. Yang, Y.W. Kao, Y.S. Lin, et al. Fixed-dose combination of amlodipine and atorvastatin improves clinical outcomes in patients with concomitant hypertension and dyslipidemia. *J Clin Hypertens (Greenwich)*, vol. 22, pp.1846-1853, 2020.

[11] R. Webster, A. Murphy, H. Bygrave, E. Ansbro, D.E. Grobbee, P. Perel. Implementing fixed dose combination medications for the prevention and control of cardiovascular diseases. *Glob Heart*, vol. 15, pp. 57, 2020

[12] O. J. Phung, D.M. Sobieraj, S.S. Engel, S.N. Rajpathak. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. *Diabetes Obes Metab*, vol.16, pp.410-417, 2014

[13] A.J. Scheen. Drug-drug interactions with sodium-glucose cotransporters type 2 (SGLT2) inhibitors, new oral glucose-lowering agents for the management of type 2 diabetes mellitus. *Clin Pharmacokinet*, vol. 53, pp. 295-304, 2014.

[14] S. Kalra, J. Kesavadev, M. Chadha, G.V. Kumar. Sodium-glucose cotransporter-2 inhibitors in combination with other glucose-lowering agents for the treatment of type 2 diabetes mellitus. *Indian J Endocrinol Metab*, vol. 22, pp. 827-836, 2018.

[15] K.S. Hershon. Options for empagliflozin in combination therapy in type 2 diabetes mellitus. *Int J Gen Me*d, vol.9, pp. 155-172, 2016.

[16] K. Kaku, H. Maegawa, Y. Tanizawa, A. Kiyosue, Y. Ide Y, T. Tokudome, et al.. Dapagliflozin as monotherapy or combination therapy in Japanese patients with type 2 diabetes: an open-label study. *Diabetes Ther*, vol.5, pp. 415-433, 2014.

[17] R.A. DeFronzo, R. Eldor, M. Abdul-Ghani. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. *Diabetes Care*, vol. 36 (Suppl 2), pp. S127-S138, 2011.

[18] C.M. Kuecker, E.M. Vivian, Patient considerations in type 2 diabetes - role of combination dapagliflozin-metformin XR. *Diabetes Metab Syndr Obes*, vol. 9, pp. 25-35, 2016.

[19] E. Ferrannini, E. Niemoeller, T. Dex, S. Servera, A. Mari. Fixed-ratio combination of insulin glargine plus lixisenatide (iGlarLixi) improves ß-cell function in people with type 2 diabetes. *Diabetes Obes Metab*, vol. 24, pp. 1159-1165, 2022

[20] H. Steinberg, M.S. Anderson, T. Musliner, M.E. Hanson, S.S. Engel. Management of dyslipidemia and hyperglycemia with a fixed-dose combination of sitagliptin and

simvastatin. *Vasc Health Risk Manag*, vol. 9, pp. 273-282, 2013

[21] Report of International Control Board for 2010. Chapter 1. *Drugs and corruption*, 2010, pp 1-13

[22] M. Sardella, G. Belcher, C. Lungu, T. Ignoni, M. Camisa, D.I. Stenver, et al. Monitoring the manufacturing and quality of medicines: a fundamental task of pharmacovigilance. *Ther Adv Drug Saf*, vol.12, 20420986211038436, 2021

[23] R. Webster, A. Salam, H.A. de Silva, V. Selak, S. Stepien, S. Rajapakse, et al. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: A randomized clinical trial. *JAMA*, vol. 320, pp.566-579, 2018

[24] A.K. Böhm, U. Schneider, J. Aberle , T. Stargardt. Regimen simplification and medication adherence: Fixed-dose versus loose-dose combination therapy for type 2 diabetes. *PLoS One*, vol. 16, :e0250993, 2021

[25] J. O'Shaughnessy, S. Sousa, J. Cruz, L. Fallowfield, P. Auvinen, C. Pulido, A. Cvetanovic A, et al. Preference for the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection in patients with HER2-positive early breast cancer (PHranceSCa): A randomised, open-label phase II study. *Eur J Cancer*, vol.152, pp. 223-232, 2021

[26] C. Jackisch, F. Manevy, S. Frank, N. Roberts, J. Shafrin J. White Paper on the Value of Time Savings for Patients and Healthcare Providers of Breast Cancer Therapy: The Fixed-Dose Combination of Pertuzumab and Trastuzumab for Subcutaneous Injection as an Example. *Adv Ther*, vol. 39, pp. 833-844, 2022.

[27] S. Belew, S. Suleman, T. Mohammed, Y. Mekonnen, M. Duguma, H. Teshome H, et al. Quality of fixed dose artemether/lumefantrine products in Jimma Zone, Ethiopia. *Malar J*, vol. 18, pp.236, 2019

[28] A. Murphy, R. Willis, É Ansbro, S. Masri, V. Kabbara, T. Dabbousy , S. Bahous S, et al. Implementation of fixed-dose combination therapy for secondary prevention of atherosclerotic cardiovascular disease among Syrian refugees in Lebanon: a qualitative evaluation. *BMC Health Serv Res*, vol. 22, pp.744, 2022.

[29] N.R. Vinnakota, V. Krishna, V. Viswanath, Z. Ahmed, K.S. Shaik, N.K. Boppana. Assessment of knowledge, attitude, and practices on fixed dose combinations among postgraduate dental students. *J Int Soc Prev Community Dent*, vol. 6(Suppl 3)pp. S243-S247, 2016.

[30] N. Goswami, A. Gandhi, P. Patel, R. Dikshit. An evaluation of knowledge, attitude and practices about prescribing fixed dose combinations among resident doctors. *Perspect Clin Res*, vol. 4, pp.130-135, 2013.